A STUDY OF "PREDICTORS AND FACTORS AFFECTING OUTCOME IN DIABETIC KETOAIDOSIS PATIENTS"

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DECLARATION

I solemnly declare that the dissertation titled **"*A STUDY OF PREDICTORS AND FACTORS AFFECTING OUTCOME IN DIABETIC KETOACIDOSIS PATIENTS*"** was done by me at Government Thanjavur Medical College and Hospital, Thanjavur, from OCTOBER 2016 to MARCH 2017 under the guidance and supervision of **PROF. DR.D. NEHRU, M.D., DMRD.,** Professor and HOD, Department of General Medicine, Government Thanjavur Medical College and Hospital, Thanjavur.

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TABLES

I. INTRODUCTION

Diabetes Mellitus (DM) comprises a group of disorders characterized by insulin deficiency or resistance leading to hyperglycemia and related complications.[1] Globally, as per the prevalence estimated 422 million adults were living with DM in 2014, compared to 108 million in 1980. The global prevalence of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population.[2]

Over the past decade, diabetes prevalence has risen faster in low- and middle-income countries than in high-income countries.[2] Diabetes caused 1.5 million deaths in 2012, higher-than-optimal blood glucose which caused an additional 2.2 million deaths, by increasing the risks of cardiovascular and other diseases. Forty-three percent of these 3.7 million deaths occur before the age of 70 years.[2]

Diabetic Ketoacidosis (DKA) is the most serious hyperglycemic emergency in patients with DM and is associated with significant morbidity and mortality.[3] The annual incidence ranges from 4.6 to 8 cases per 1,000 diabetic patients.[4]DKA is responsible for more than 500,000 cases hospitalised days per year .[5,6] National Centre for health statistics showed that most patients with DKA were between the ages of 18 and 44 years (56%) and 45 and 65 years (24%), with only 18% of patients <20 years of age.[5]

DKA is associated with a mortality rate of 2% to 10% [4], while the mortality rates of hyperglycemic emergencies in Sub-Saharan Africa and Asia range from 30% to 44%.[4,7,9] The estimated mortality rate of DKA ranges between 5% to 10%, and the rate of hyperosmolar hyperglycemic syndrome varies from 10% to 50% .[8]

Mortality in hyperglycemic crisis is primarily due to the underlying precipitating illness and only rarely to the metabolic complications of hyperglycemia or ketoacidosis .[3]The prognosis of hyperglycemic crisis is substantially worse at the extremes of age and in the presence of coma and hypotension .[10-13]So, in this study we tried to find out the predictors of DKA and try to find out the effect of different confounding covariates at presentation on final outcome .

II-REVIEW OF LITERATURE

DIABETES MELLITUS is a group of chronic non-communicable disorders characterised by increased plasma glucose levels above defined normal limits.[1]It is associated with a relative or absolute impairment in insulin secretion, along with varying degrees of peripheral resistance to the action of insulin.[1]

CLINICAL PRESENTATION — Classic symptoms of hyperglycemia include polyuria, polydipsia, nocturia, blurred vision, and, infrequently, weight loss. These symptoms are often noted only in retrospect after a blood glucose value has been shown to be elevated.[14]Polyuria occurs when the serum glucose concentration rises significantly above 180 mg/dL leading to glycosuria causing osmotic diuresis, which in turn can lead to polydipsia.[14]

The adults with DM can also present with features of hyperosmolar hyperglycemic state or diabetic ketoacidosis.

DIAGNOSTIC CRITERIA OF DIABETES

- *Symptoms of hyperglycemia* — The diagnosis of Diabetes Mellitus is easily established when a patient presents with classic symptoms of hyperglycemia and has a random blood glucose value of 200 mg/dL (11.1 mmol/L) or higher.[15-17]
- *Asymptomatic* — The diagnosis of diabetes in an asymptomatic individual can be established with any of the following criteria : [15-17]

  ●Fasting plasma glucose (FPG) values ≥126 mg/dL (7.0 mmol/L)

  ●Two-hour plasma glucose values of ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT)

  ●A1C values ≥6.5 percent (48 mmol/mol)

In case of equivocal results, the diagnosis of diabetes must be confirmed on a subsequent day by repeat measurement of same test or a different test.

AMERICAN DIABETES ASSOCIATION DEFINITIONS

The following definitions are from the American Diabetes Association (ADA) reports:[16-18,20,21]

- Normal – FPG <100 mg/dL (5.6 mmol/L). Two-hour glucose during OGTT <140 mg/dL (7.8 mmol/L).
- Categories of increased risk for diabetes:
  - IFG – FPG between 100 and 125 mg/dL (5.6 to 6.9 mmol/L).
  - IGT – Two-hour plasma glucose value during a 75 g OGTT between 140 and 199 mg/dL (7.8 to 11.0 mmol/L).
  - A1C – Persons with 5.7 to 6.4 percent (39 to 46 mmol/mol), (6.0 to 6.4 percent [42 to 46 mmol/mol] in the International Expert Committee report)[19] are at highest risk, although there is a continuum of increasing risk across the entire spectrum of A1C levels less than 6.5 percent (48 mmol/mol).
- Diabetes Mellitus – FPG at or above 126 mg/dL (7.0 mmol/L), A1C ≥6.5 percent (48 mmol/mol), a two-hour value in an OGTT at or above 200 mg/dL (11.1 mmol/L), or a random (or "casual") plasma glucose concentration ≥200 mg/dL (11.1 mmol/L) in the presence of symptoms.

CLASSIFICATION OF DIABETES:[22]

1.Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)

a) Immune-mediated

b) Idiopathic

2.Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

3.Other specific types

A. Genetic defects of beta cell function

- Chromosome 12, HNF-1-alpha (MODY3);
- Chromosome 7, glucokinase (MODY2);
- Chromosome 20, HNF-4-alpha (MODY1);
- Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4);
- Chromosome 17, HNF-1-beta (MODY5);
- Chromosome 2, NeuroD1 (MODY6);
- Mitochondrial DNA,
- Others .

B. Genetic defects in insulin action-

- Type A insulin resistance,
- Leprechaunism,

- Rabson-Mendenhall syndrome,
- Lipoatrophic diabetes,
- Others.

C. Diseases of the exocrine pancreas –

- Pancreatitis,
- Trauma/pancreatectomy,
- Neoplasia,
- Cystic fibrosis,
- Hemochromatosis,
- Fibrocalculous pancreatopathy,
- Others

D. Endocrinopathies

- Acromegaly,
- Cushing's syndrome,
- Glucagonoma,
- Pheochromocytoma,
- Hyperthyroidism,
- Somatostatinoma,
- Aldosteronoma,
- Others

E. Drug or chemical induced-

- Vacor,
- Pentamidine,
- Nicotinic acid,
- Glucocorticoids,
- Thyroid hormone,
- Diazoxide,
- Beta-adrenergic agonists,
- Thiazides,
- Dilantin,
- Alpha-Interferon,
- Others

F. Infections-

- Congenital rubella,
- Cytomegalovirus,
- Others

G. Uncommon forms of immune-mediated diabetes-

- "Stiff man" syndrome,
- Anti-insulin receptor antibodies,
- Others

H. Other genetic syndromes sometimes associated with diabetes-

- Down's syndrome,
- Klinefelter's syndrome,
- Turner's syndrome,
- Wolfram's syndrome,
- Freiderich's ataxia,
- Huntington's chorea,
- Laurence-Moon-Biedl syndrome,
- Myotonic dystrophy,
- Porphyria,
- Prader-Willi syndrome,
- Others

4.Gestational diabetes mellitus

DISTINGUISHING TYPE 1 AND 2 DM-

Type 1 diabetes is characterized by destruction of the pancreatic beta cells, leading to absolute insulin deficiency. This is usually due to autoimmune destruction of the pancreatic beta cells.[23]

Type 2 diabetes is by far the most common type of diabetes, and is characterized by variable degrees of insulin deficiency and resistance.

It is occasionally difficult to distinguish between type 1 and atypical presentations of type 2 diabetes (i.e., thin patient with poor response to initial therapy with sulfonylureas or metformin, personal or family history of autoimmune disease).[24]In these cases, two to three autoantibodies (GAD65, insulin, tyrosine phosphatases [insulinoma-associated protein 2 {IA-2} and IA-2 beta], islet cell, or ZnT8) are measured.[25] If one or more of the antibodies is present, and especially if two or more are positive, the patient should be presumed to have type 1 diabetes and should be treated with insulin replacement therapy, as these patients respond poorly to diet and oral hypoglycemic drug therapy.[25-27]

Patients with Latent Autoimmune Diabetes In Adults (LADA) are a heterogeneous group of patients with variable titers of antibodies, body mass index (BMI), and frequency of progression to insulin dependence.[28]

In genotyping analyses, LADA shares genetic features of both type 1 and type 2 diabetes.[30-32] Patients with high compared with low titers of GAD65

antibodies usually have a lower BMI, less endogenous insulin secretion and progress more quickly to insulin dependence.[28,29]

KETOSIS-PRONE DIABETES (KPD)-

It is an emerging heterogeneous syndrome characterized by the presence of diabetic ketoacidosis (DKA) in patients who may lack the typical clinical phenotype of autoimmune type 1 diabetes. Among patients presenting with DKA (absolute insulin deficiency), those who lack autoantibodies are referred to as "idiopathic type 1" or "type 1b"; the latter includes patients with the clinical appearance of type 2 diabetes, with some becoming insulin independent.[33]

CLASSIFIFICATION OF KPD

Aß system

Aß classification distinguishes four KPD subgroups based on the presence or absence of autoantibodies and the presence or absence of beta cell functional reserve, as measured by a fasting or glucagon-stimulated C-peptide level.

The classes are :[34]

- A+ß- autoantibodies present, beta cell function absent
- A+ß+ autoantibodies present, beta cell function present
- A-ß- autoantibodies absent, beta cell function absent
- A-ß+ autoantibodies absent, beta cell function present

A+ß- and A-ß- represents type 1and type1 b DM , while A+ß+ and A-ß+ are genetically different but share the clinical characteristics of type 2 DM.[33]

ACUTE DISORDERS RELATED TO HYPERGLYCEMIA

Diabetic ketoacidosis (DKA) and **hyperosmotic hyperglycemic nonketotic state [HHNK]** are the most serious acute complications of diabetes. DKA is characterized by ketoacidosis and hyperglycemia, while HHS has more severe hyperglycemia but no ketoacidosis.[3,35,36] The diagnostic criteria proposed by the American Diabetes Association (ADA) for mild, moderate, and severe DKA and HHS are shown in the table below :

TABLE 1: Diagnostic criteria for DKA and HHS

	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Plasma glucose (mmol/L)	>13.9	>13.9	>13.9	>33.3
Arterial pH	7.25 to 7.30	7.00 to 7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15 to 18	10 to <15	<10	>18
Urine ketones¶	Positive	Positive	Positive	Small
Serum ketones - Nitroprusside reaction	Positive	Positive	Positive	≤ Small
Serum ketones - Enzymatic assay of beta hydroxybutyrate (normal range <0.6 mmol/L)Δ	3 to 4 mmol/L	4 to 8 mmol/L	>8 mmol/L	<0.6 mmol/L
Effective serum osmolality (mOsm/kg)◇	Variable	Variable	Variable	>320
Anion gap§	>10	>12	>12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

DKA: diabetic ketoacidosis; HHS: hyperosmolar hyperglycemic state.
* There may be considerable diagnostic overlap between DKA and HHS.
¶ Nitroprusside reaction method.
Δ NOTE: Many assays for beta hydroxybutyrate can only report markedly elevated values as >6.0 mmol/L.
◇ Calculation: 2[measured Na (mEq/L)] + glucose (mg/dL)/18.
§ Calculation: (Na+) – (Cl– + HCO3–) (mEq/L). See text for details.

NOTE: *2006 American Diabetes Association. From Diabetes Care Vol 29, Issue 12, 2006. Information updated from Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009; 32:1335.*

PATHOGENESIS

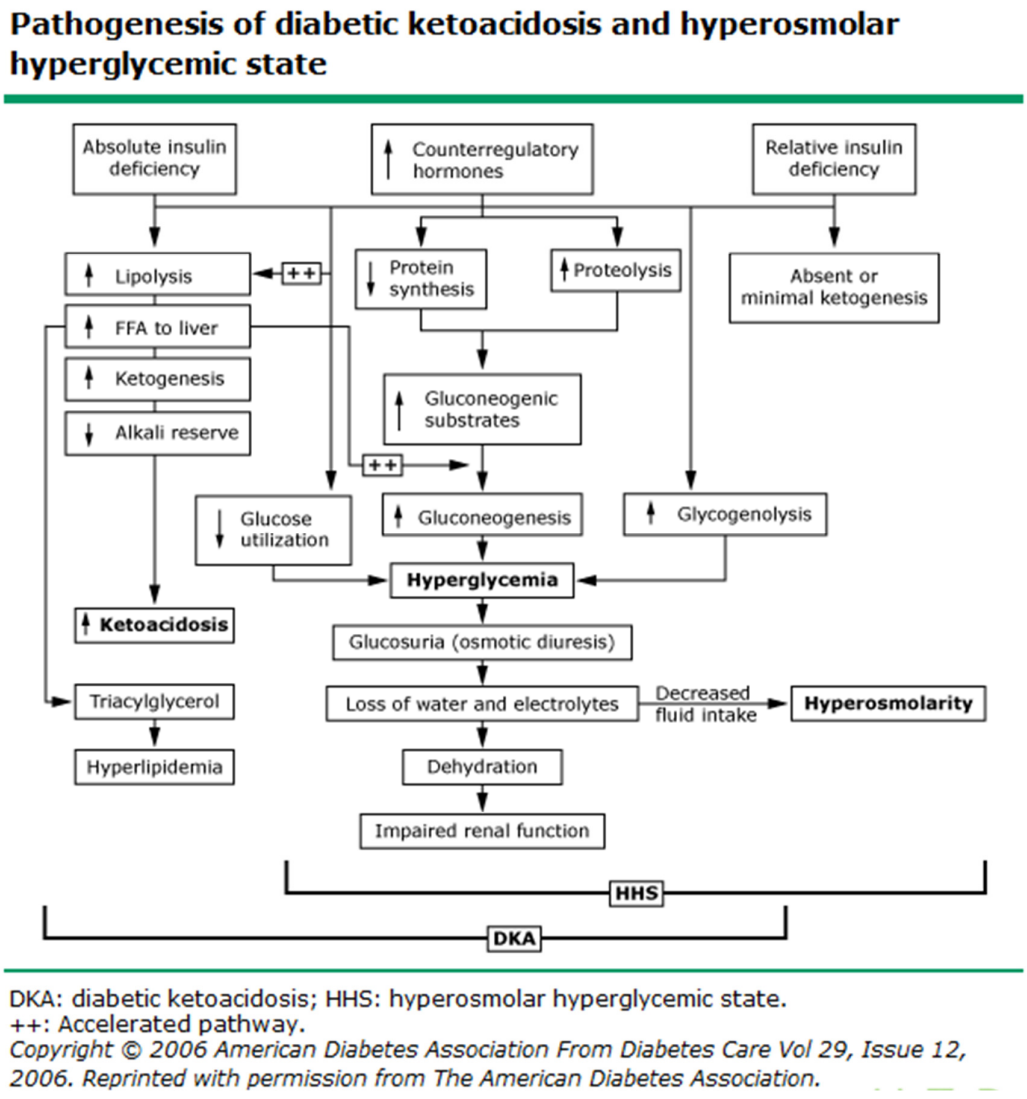
i)Normal response to hyperglycemia - The extracellular concentration of glucose is primarily regulated by two hormones: insulin and glucagon. After a carbohydrate meal, as the blood glucose level rises, insulin is released from beta cells of pancreas. Insulin restores normoglycemia by inhibiting glycogenolysis and gluconeogenesis in liver and by increasing glucose uptake by skeletal muscle and adipose tissue. Insulin inhibits glucagon secretion by acting on glucagon gene in the pancreatic alpha cells .[37,38,39]

ii)Spectrum of metabolic abnormalities — The primary hormonal abnormalities linked with hyperglycemic emergencies are Insulin deficiency and/or resistance and Glucagon excess .[37,38,46] In addition, increased secretion of catecholamines, cortisol, and growth hormone, which oppose the actions of insulin, also contribute to the increases in glucose and ketoacid production .[3]

The deficiency in insulin is more severe in DKA compared with HHS. Since suppression of lipolysis and ketogenesis is more sensitive to insulin than the inhibition of gluconeogenesis, the residual insulin secretion and its systemic activity in HHS is sufficient to prevent ketoacidosis but not hyperglycemia.[3]

In patients with absolute or relative insulin deficiency, DKA and HHS are usually precipitated by stresses that act in part by increasing the secretion of glucagon, catecholamines, and cortisol.

FIGURE 1- Pathogenesis of DKA and HHS



DKA: diabetic ketoacidosis; HHS: hyperosmolar hyperglycemic state.
++: Accelerated pathway.

note: American Diabetes Association From Diabetes Care Vol 29, Issue 12, 2006.

iii)Hyperglycemia — The serum glucose concentration in HHS frequently exceeds 1000 mg/dL (56 mmol/L), but in DKA is generally below 800 mg/dL (44 mmol/L) and often in the 350 to 450 mg/dL (19.4 to 27.8 mmol/L) range.[40]

The factors that lead to less severe hyperglycemia in DKA are early presentation due to acuity of illness and most of these patients are younger with supranormal glomerular filtration rate in early years causing severe glucosuria.[40,41,42,43]

Hormonal alterations in DKA and HHS generate hyperglycemia by their impact on three fundamental processes in glucose metabolism:[3,44,45]

- Impaired glucose utilization in peripheral tissues
- Increased hepatic and renal gluconeogenesis
- Increased glycogenolysis

Insulin deficiency and/or resistance promote and accelerate hepatic gluconeogenesis by increasing the delivery of gluconeogenic precursors to the liver, activating the enzymes in the gluconeogenic pathway and increasing the secretion of glucagon.[37,38,39]Oxidation of fatty acids, provides the metabolic energy required to drive gluconeogenesis.[46,47,48]

iv)Ketone production — The insulin deficiency is essential and glucagon excess is contributory to the genesis of DKA.[49,47,50] Insulin deficiency and resistance causes enhanced lipolysis from peripheral fat stores, due to the activity of hormone sensitive lipase which releases free fatty acids and glycerol. The fatty acids are transported, bound to albumin and are taken up by hepatocytes. Within the hepatocyte cytoplasm, acyl-CoA (ie, fatty acid-CoA) if formed, which is transported into the mitochondria. by a pair of carnitine palmityl transferase reactions.[46,47,50-54]

Within the mitochondria, beta-oxidation splits the fatty acids into multiple two-carbon units of acetyl-CoA which can enter the Krebs cycle to produce adenosine triphosphate (ATP) or used to synthesize fatty acids or enter the ketogenic metabolic path to form acetoacetic acid.

When fatty acid delivery to the mitochondria is high, the accumulating acetyl-CoA instead is converted to acetoacetic acid, the first "ketone body". The acetoacetic acid may then be reduced to beta-hydroxybutyric, or nonenzymatically decarboxylated to acetone[55]. Ketones provides alternate energy in states of reduced glucose availability.

The absence of ketogenesis in HHS is due to the differential sensitivity of fat metabolism and glucose metabolism to the effects of insulin. Thus, more moderate insulin deficiency, as occurs in HHS, is sufficient to minimize lipolysis (and so ketoacid formation) but not enough to block gluconeogenesis,

promote glucose utilization, and thereby prevent the development of hyperglycemia.[56] More severe insulin deficiency generates ketoacidosis.

v)Anion gap metabolic acidosis — DKA typically presents as an elevated anion gap metabolic acidosis. This is caused by the production and accumulation of beta-hydroxybutyric and acetoacetic acids.

Serum anion gap = serum sodium - (serum chloride + bicarbonate)[57]

The severity of the metabolic acidosis is dependent upon a number of factors:

- The rate and duration of ketoacid production.
- The rate of metabolism of the ketoacids.
- The rate of loss of ketoacid anions in the urine.
- The volume of distribution of the ketoacid anions.
- The rate of renal net acid excretion.

In a study of patients with DKA: ketone production averaged 51 mEq/hour,while net acid excretion with the ketoacid anions averaged 15 mEq/hour or 30 percent of the ketoacid load.[58] The conversion of acetoacetic acid to acetone can neutralize another 15 to 25 percent of the acid load. [58,59]

Renal excretion of ketoacid anions increases when patients are treated with intravenous isotonic fluids to correct the hypovolemia.

Excretion of ketoacid anions reduces the anion gap, but to the extent that they are excreted as sodium and potassium salts, the severity of the systemic acidemia is unchanged. [60,61,62,63]Sodium or potassium ketoanion salts represent both "decomposed" bicarbonate and also "potential bicarbonate." [64]When the ketoacids are generated, the protons combine with bicarbonate to form carbon dioxide (CO_2) and essentially bicarbonate anions in the serum are replaced with ketoacid anions ("decomposed bicarbonate").[64] If the ketoacid anions are metabolized, then a bicarbonate anion is regenerated ("potential bicarbonate").[64] Therefore, the urinary loss of ketoacid anions as sodium or potassium salts represents the loss of "potential bicarbonate."[64] Furthermore, the loss of beta-hydroxybutyrate and acetoacetate as sodium and potassium salts will reduce the anion gap and convert the anion gap acidosis to a hyperchloremic, or non-gap, acidosis.[64] Thus, almost all patients with diabetic ketoacidosis who have relatively intact renal function will develop a hyperchloremic (normal anion gap) metabolic acidosis when they are treated with isotonic saline and insulin, due to the urinary loss of potential bicarbonate.[64]

A small but clinically significant fraction of ketoacids, acetone and dihydroxyacetone phosphate (a product of glycolysis) can each be converted to D-lactic acid.[65] D-lactic acid can account for as much as 8 to 10 mEq/L of the anion gap elevation and bicarbonate reduction in patients with severe DKA.[65]

vi)Plasma osmolality and sodium — Plasma osmolality is always elevated in patients with HHS but less so with DKA. The increase in plasma osmolality created by hyperglycemia, loss of electrolyte free water and high plasma acetone.[40]

The measured serum sodium concentration in uncontrolled diabetes mellitus is affected by hyperglycemia, which dilutes the serum sodium concentration; glucosuria generating electrolyte-free water in the urine will raise the serum sodium concentration; and variable intake of water and the loss of free water in vomitus or naso-gastric suction will also impact the serum sodium concentration.[64]It is estimated that the sodium should fall by about 2.4 mEq/L for each 100 mg/100 mL (5.5 mmol/L) increase in glucose concentration.[66.67]

vii)Potassium — Patients presenting with DKA or HHS have a potassium deficit that averages 300 to 600 mEq.[64] Factors contributing to this deficit are increased urinary losses due both to the glucose osmotic diuresis and the excretion of potassium ketoacid anion salts.[64] Gastrointestinal losses and the loss of potassium from the cells due to glycogenolysis and proteolysis also may play a contributory role.[64]

Despite these large total body potassium deficits, the serum potassium concentration is usually normal or elevated on admission due to

hyperosmolality and insulin deficiency causing potassium shift from ICF to ECF.[40,44,68,71]A little role is played by acidemia in this shift. [64]

viii)Inflammation — Hyperglycemic crises are proinflammatory states that lead to generation of reactive oxygen species and oxidative stress.[64] Studies have shown elevated pro-inflammatory cytokines including tumor necrosis factor-alpha and interleukin (IL)-1B, IL-6, and IL-8, lipid peroxidation markers, plasminogen activator inhibitor-1 and C-reactive protein (CRP) are also increased.[72] Proinflammatory factors returned to near normal levels within 24 hours of insulin therapy and resolution of hyperglycemia.[64] The proinflammatory state in DKA results in in vivo activation of T-lymphocytes with de novo emergence of growth factor receptors.[73]

A variety of eicosanoids, including prostaglandins, are involved in the pathogenesis of diabetes mellitus and its complications.[74] Some are protective and others accelerate organ dysfunction, including pancreatic beta-cell destruction.[64] Prostaglandins accumulate during DKA, increase in the circulation before epinephrine, and return promptly to normal levels with insulin therapy.[75,76]

A precipitating event can usually be identified in patients with diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS)[77-79]. The most common events are infections of respiratory tract or urinary tract and discontinuation of or inadequate insulin therapy. Compromised water intake due

to underlying medical conditions, particularly in older patients, can promote the development of severe dehydration and HHS[79-81].

Other conditions and factors associated with DKA and HHS include:

- Acute major illnesses such as myocardial infarction, cerebrovascular accident, sepsis, or pancreatitis.
- New onset type 1 diabetes, in which DKA is a common presentation.
- In established type 1 diabetes, omission of insulin in setting of gastroenteritis when patient mistakenly stops insulin because of reduced oral intake.
- Drugs that affect carbohydrate metabolism, including glucocorticoids, higher-dose thiazide diuretics, sympathomimetic agents[82], and second-generation "atypical" antipsychotic agents[83]
- SGLT2 inhibitors, mostly used in type 2 diabetes but also used off-label in type 1 diabetes[84]
- Cocaine use, which has been associated with recurrent DKA[85,86].
- Psychological problems associated with eating disorders and purposeful insulin omission, particularly in young patients with type 1 diabetes[87]. Factors that may lead to insulin omission in younger patients include fear of weight gain, fear of hypoglycemia, rebellion from authority, and the stress of chronic disease.
- Poor compliance with the insulin regimen.

●Pump malfunction is now uncommon, but system failure due to blockage or leakage in the syringe or the infusion set or connectors, causing an interruption of infusion flow infusion set, can lead to DKA. The frequency of DKA with pump therapy, however, appears to be no different from that with multiple daily injections of insulin[88].

CLINICAL PRESENTATION OF DKA

DKA usually evolves rapidly, over a 24-hour period, whereas, HHS develops more insidiously with polyuria, polydipsia, and weight loss, often persisting for several days before hospital admission[89].

The earliest symptoms of marked hyperglycemia are polyuria, polydipsia, and weight loss. As the degree or duration of hyperglycemia progresses, neurologic symptoms, including lethargy, focal signs, and obtundation, can develop , progressing in to coma. Neurologic symptoms are most common in HHS, while hyperventilation and abdominal pain are primarily limited to patients with DKA.[89]

Neurologic symptoms — Neurologic deterioration primarily occurs in patients with an effective plasma osmolality above 320 to 330 mosmol/kg.[77,90,91] Mental obtundation and coma are more frequent in HHS than DKA because of the usually greater degree of hyperosmolality in HHS.[92]In addition, some patients with HHS have focal neurologic signs and/or seizures.[92-96] Mental obtundation

may occur in patients with DKA, who have lesser degrees of hyperosmolality, when severe acidosis exists.[97] However, stupor or coma in diabetic patients with an effective plasma osmolality lower than 320 mosmol/kg demands immediate consideration of other causes of the mental status change.[89]

Abdominal pain in DKA — Patients with DKA present with nausea, vomiting, and abdominal pain. Abdominal pain is unusual in HHS. In a review of 189 consecutive episodes of DKA and 11 episodes of HHS, abdominal pain was reported in 46 percent of patients with DKA compared with none of the patients with HHS[98]. Abdominal pain was associated with the severity of the metabolic acidosis but did not correlate with the severity of hyperglycemia or dehydration.[98]

Possible causes of abdominal pain include delayed gastric emptying and ileus induced by the metabolic acidosis and associated electrolyte abnormalities[77]. Other causes for abdominal pain, such as pancreatitis, should be sought when, in the absence of severe metabolic acidosis.[89]

Physical examination — Signs of volume depletion are common in both DKA and HHS and include decreased skin turgor, dry axillae and oral mucosa, low jugular venous pressure, tachycardia, and, if severe, hypotension. Neurologic findings may also be present particularly in patients with HHS.[89]

Patients with DKA may have a fruity odour and Kussmauls respirations reflecting the compensatory hyperventilation to acidosis.[89]

DIAGNOSTIC EVALUATION OF DKA—

The initial evaluation of patients with hyperglycemic crises should include assessment of cardiorespiratory status, volume status, and mental status. The initial history and rapid but careful physical examination should focus on:[89]

- Airway, breathing, and circulation (ABC) status
- Mental status
- Possible precipitating events (eg, source of infection, myocardial infarction)
- Volume status

The initial laboratory evaluation of a patient with suspected DKA or HHS should include determination of:[89]

- Serum glucose
- Serum electrolytes
- Renal function tests
- Complete blood count (CBC) with differential
- Urinalysis and urine ketones by dipstick
- Plasma osmolality
- Serum ketones
- Arterial blood gas
- Electrocardiogram

Additional testings, such as cultures of urine, sputum, and blood, serum lipase and amylase and chest radiograph should be performed based on need. If infection is suspected, appropriate cultures should be obtained.

Measurement of glycated hemoglobin (A1C) is useful to determine whether the acute episode is the culmination of an evolutionary process in a poorly controlled diabetes or a truly acute episode in an otherwise well-controlled patient.[89]

Laboratory findings — Hyperglycemia and hyperosmolality are the two primary laboratory findings in patients with DKA or HHS; patients with DKA also have a high anion gap metabolic acidosis.[3]

A variety of other laboratory tests are affected due to the impact of hyperglycemia, insulin deficiency, osmotic diuresis, and fluid intake in each individual patient .

i) Serum glucose — The serum glucose concentration frequently exceeds 1000 mg/dL (56 mmol/L) in HHS,[90,99] but is generally around 350 to 500 mg/dL (19.4 to 27.8 mmol/L) in DKA.[99,100]

Euglycemic or minimally hyperglycemic DKA, has been described in patients with poor oral intake, treatment with insulin prior to arrival in the emergency department, or in pregnant women.[101-103]

It has also been described in patients treated with the class of drugs that block the sodium/glucose cotransporter 2 (SGLT2 inhibitors) minimize hyperglycemia by producing glucosuria.[3]

ii) Serum ketones — Three ketone bodies are produced and accumulate in DKA: acetoacetic acid, a true ketoacid; beta-hydroxybutyric acid ; and acetone, a true ketone. Urine ketone bodies are detected with nitroprusside tests, while serum ketones can[89] be detected with either a nitroprusside test or by direct assay of beta-hydroxybutyrate levels. Direct assay of beta-hydroxybutyrate levels is preferred for monitoring response to therapy. [3]

iii) Anion gap metabolic acidosis — The serum anion gap is calculated as follows:[89]

Serum anion gap = Serum sodium - (serum chloride + bicarbonate)

By convention, it is the actual measured plasma sodium concentration and not the sodium concentration corrected for the simultaneous glucose concentration that is used for this calculation.[89]

The serum bicarbonate concentration in DKA is usually moderately-to-markedly reduced with a serum anion gap greater than 20 mEq/L (normal -3 to 10 mEq/L) due to accumulation of beta-hydroxybutyric and acetoacetic acids. In contrast, the serum bicarbonate concentration is normal or mildly reduced in HHS. Compensatory hyperventilation reduces the partial pressure of carbon

dioxide (CO2) and mitigates the fall in arterial pH. However, severe ketoacidosis can reduce the pH below 7.0 .[89]

iv) Plasma osmolality — Plasma osmolality is always elevated in patients with HHS but less so with DKA. In patients with HHS, the effective plasma osmolality is typically >320 mosm/kg.

Effective plasma osmolality (Posm, in mosmol/kg) is the portion of total osmolality which is generated by sodium salts and glucose, which can cause movement of water across membranes to achieve osmolal equilibrium. Effective plasma osmolality does not include "ineffective" osmoles, such as urea.[104]

Effective Posm = [2 x Na (mEq/L)] + [glucose (mg/dL) ÷ 18]

The Na is the actual measured plasma sodium concentration .

If the plasma osmolality is measured, using a freezing point reduction osmometer, the result is the total osmolality. Because effective osmolality excludes urea osmoles (BUN), it can be estimated as:[89]

Effective Posm = Measured Posm - BUN (mmol/L)

v) Serum sodium — Most patients with DKA and HHS are mildly hyponatremic.[105]However, patients with HHS who have a marked osmotic diuresis may present with a normal or even elevated serum sodium concentration.[106]

The measured serum sodium concentration in uncontrolled diabetes mellitus is variable because of the interaction of multiple factors. The increase in plasma osmolality created by hyperglycemia pulls water out of the cells, and reduces the plasma sodium concentration. Physiologic calculations suggest that, in the absence of urine losses, the serum sodium concentration should fall by about 1.6 mEq/L for each 100 mg/100 mL (5.5 mmol/L) increase in glucose concentration. So, the "corrected" sodium concentration can be approximated by adding 2.0 mEq/L to the plasma sodium concentration for each 100 mg/100 mL increase above normal glucose concentration .[89]

vi) Pseudohyponatremia/pseudohyperchloremia — Some patients with uncontrolled diabetes develop marked hyperlipidemia and have lactescent serum. This can create electrolyte artifacts when certain analyzers are utilized. Hyperlipidemia will displace water and thereby reduce the plasma water phase fraction below its normal 93 percent. If any step in the analysis requires an exact volume of plasma , then a reduced amount of water will be analyzed. This can result in "pseudohyponatremia." This artifact occurs with any flame photometric analysis and most indirect potentiometric or ion selective electrode methods. However, direct potentiometry analytical methods are generally not susceptible to this artifact.[89]

However, hyperlipemia can have an opposite artifactual effect on the chloride concentration when certain chloride analyzers are employed, generating marked pseudohyperchloremia .[89]

vii) Serum potassium — Patients presenting with DKA or HHS have a potassium deficit that averages 300 to 600 mEq.[105,107,108] Factors contributing to this deficit are increased urinary losses due to glucose osmotic diuresis and excretion of potassium ketoacid anion salts. Despite these total body potassium deficits, hypokalemia is observed in only 5 percent of cases.[109,110] This is mainly due to a shift of potassium from intracellular fluid to extracellular fluid caused by hyperosmolality and insulin deficiency.[82,104,105]

Insulin therapy shifts potassium into cells and can result in severe hypokalemia[108]. S potassium should be carefully monitored and supplemented

viii) Serum phosphate — Patients with uncontrolled hyperglycemia are typically in negative phosphate balance because of decreased phosphate intake, an acidosis-related shift of phosphate into the extracellular fluid (ECF) when metabolic acidosis exists, and phosphaturia caused by osmotic diuresis. Despite phosphate depletion, the serum phosphate concentration at presentation is usually normal or even high because both insulin deficiency and metabolic acidosis cause a shift of phosphate out of the cells and as a

result of ECF volume contraction.[111,112]This transcellular shift is reversed and the true state of phosphate balance is unmasked after treatment with insulin and volume expansion.

ix) Serum creatinine — Most of these patients have acute elevations in the BUN and serum creatinine concentration, which reflect the reduction in glomerular filtration rate induced by hypovolemia.

x) Serum amylase and lipase — Acute pancreatitis may precipitate or complicate DKA. Serum amylase and lipase are generally used to diagnose acute pancreatitis, but each of these enzymes is often elevated in patients with DKA who do not have any other clinical or radiological evidence of pancreatitis.[113-117]Therefore, the diagnosis of pancreatitis in patients with DKA should be primarily based upon clinical findings and imaging.

xi) Leukocytosis — The majority of patients with hyperglycemic emergencies present with leukocytosis, which is proportional to the degree of ketonemia.[82,118] However, a white blood cell count greater than 25,000/microL or more than 10 percent bands increases suspicion for infection and should be evaluated.[119]

x) Lipids — Patients with DKA or HHS may present with marked hyperlipidemia and lactescent serum.[120] Lipolysis in DKA, and to a lesser extent in HHS, is due to insulin deficiency, combined with elevated levels of lipolytic hormones (catecholamines, growth hormone, corticotropin [ACTH], and glucagon). Lipolysis releases glycerol and free fatty acids into the circulation. High levels of serum fatty acids inhibit glycolysis, and in the hepatocyte mitochondria is the substrate for ketoacid generation. Insulin is the most potent anti-lipolytic hormone.[89]

TREATMENT

(i) Fluid replacement — In patients with DKA or HHS, early vigorous IV electrolyte and fluid replacement is advised to correct both hypovolemia and hyperosmolality.Fluid repletion is usually initiated with isotonic saline (0.9 % sodium chloride [NaCl]) and is dependent upon the clinical state of the patient.[121]

In hypovolemic patients without shock (and without heart failure), isotonic saline is infused at a rate of 15 to 20 mL/kg lean body weight per hour, for the first couple hours, with a maximum of <50 mL/kg in the first four hours[3].

After the second or third hour, optimal fluid replacement depends upon the state of hydration, serum electrolyte levels, and the urine output. The most appropriate IV fluid composition is determined by the sodium concentration "corrected" for the degree of hyperglycemia. If the "corrected" serum sodium concentration is[3]:

- Less than 135 mEq/L, isotonic saline should be continued at a rate of approximately 250 to 500 mL/hour.
- Normal or elevated, the IV fluid is generally switched to one-half isotonic saline at a rate of 250 to 500 mL/hour in order to provide electrolyte-free water.

The concurrent potassium replacement may be another indication for the use of one-half isotonic saline as it is an osmotically active agent.[121]

The dextrose is added to the saline solution when the serum glucose reaches 200 mg/dL (11.1 mmol/L) in DKA or 250 to 300 mg/dL(13.9 to 16.7 mmol/L) in HHS. In euglycemic DKA, dextrose is added to IV fluids at the initiation of therapy.[121]

Adequate rehydration with correction of the hyperosmolar state may enhance the response to low-dose insulin therapy[122,123]. Adequacy of fluid replacement is judged by frequent hemodynamic and laboratory monitoring. In patients with abnormal renal or cardiac function, more frequent monitoring must be performed to avoid iatrogenic fluid overload[11,124-129]. The goal is to correct estimated deficits within the first 24 hours. However, osmolality should not be reduced too rapidly, because this may generate cerebral edema.

ii) Potassium replacement — Potassium replacement is initiated immediately if the serum potassium is <5.3 mEq/L.

- If the initial serum potassium is below 3.3 mEq/L, IV potassium chloride (KCl 20 to 40 mEq/hour, which usually requires 20 to 40 mEq/L added to saline) should be given. Patients with marked hypokalemia require aggressive potassium replacement (40 mEq/ hour, with additional supplementation based upon hourly serum potassium

measurements) to raise the serum potassium concentration into the normal range of 4 to 5 mEq/L[130-132].

- If the initial serum potassium is between 3.3 and 5.3 mEq/L, IV KCl (20 to 30 mEq) is added to each liter of IV replacement fluid and continued until the serum potassium concentration has increased to the 4.0 to 5.0 mEq/L range.
- If the initial serum potassium concentration is greater than 5.3 mEq/L, then potassium replacement should be delayed until its concentration has fallen below this level.

Potassium salts added to IV fluids have the same osmotic effect as sodium salts, and this should be considered when determining the potential impact of IV fluid infusion on osmolality. As an example, 40 mEq of KCl added to 1 L of fluid generates 80 mOsmol/Lof electrolyte osmolality. However, KCL will not have the same extracellular fluid (ECF) expansion effect as NaCl, because most of the potassium will shift into cells very rapidly.

The potassium replacement must be done cautiously if renal function remains depressed and/or urine output does not increase to a level >50 mL/hour. Careful monitoring of the serum potassium is essential for the management of both DKA and HHS.

iii) Insulin — A low-dose IV insulin should be started in all patients with moderate to severe DKA or HHS who have a serum potassium ≥3.3 mEq/L. Insulin administration should be delayed only in cases with serum potassium below 3.3 mEq/L since insulin will worsen the hypokalemia by driving potassium into the cells and cause Patients with an initial serum potassium below 3.3 mEq/L should receive aggressive fluid and potassium replacement prior to treatment with insulin. Insulin therapy should be delayed until the serum potassium is above 3.3 mEq/L to avoid complications such as cardiac arrhythmias, cardiac arrest, and respiratory muscle weakness[3,130,131].

IV regular insulin and rapid-acting insulin analogs are equally effective in treating DKA[133].

Insulin therapy lowers the serum glucose concentration, diminishes ketone production and augment ketone utilization. Inhibition of lipolysis requires a much lower level of insulin than that required to reduce the serum glucose concentration[124,134,135].

- Intravenous regular insulin — In HHS or moderate to severe DKA, treatment can be initiated with an IV bolus of regular insulin (0.1 units/kg body weight) followed within 5 minutes by a continuous infusion of regular insulin of 0.1 units/kg/hour[124,136-139]. Alternatively, the bolus dose can be omitted if a higher dose of continuous IV regular insulin (0.14 units/kg per hour) is initiated [29].

These doses of IV regular insulin usually decrease the serum glucose concentration by approximately 50 to 70 mg/dL (2.8 to 3.9 mmol/L) per hour[134,137-139]. However, if the serum glucose does not fall by at least 50 to 70 mg/dL from the initial value in the first hour, check the IV access to be certain that the insulin is being delivered. After this, the insulin infusion rate should be doubled every hour until a steady decline in serum glucose of this magnitude is achieved.

The fall in serum glucose is the result of both insulin activity and the beneficial effects of volume repletion. Volume repletion alone can initially reduce the serum glucose by 35 to 70 mg/dL (1.9 to 3.9 mmol/L) per hour due to ECF expansion and dilution, increased urinary losses resulting from improved renal perfusion and glomerular filtration, and an amelioration of the high "stress hormone" levels, which oppose the effects of insulin, as ECF volume is restored[127,138].

When the serum glucose reaches 200 mg/dL (11.1 mmol/L) in DKA or 250 to 300 mg/dL (13.9 to 16.7 mmol/L) in HHS, the IV saline solution is switched to dextrose in saline, and it may be possible to decrease the insulin infusion rate to 0.02 to 0.05 units/kg per hour[125,11,136]and do not allow the serum glucose at this time to fall below 200 mg/dL in DKA or 250 to 300 mg/dL in HHS, because this may promote the development of cerebral edema.

- Intravenous insulin analogs — The use of IV insulin preparations other than regular insulin was evaluated in a study of 74 patients with DKA who were randomly assigned to IV regular or glulisine insulin [22]. The initial dosing was the same in both groups (0.1 unit/kg IV bolus, followed by an infusion at 0.1 unit/kg per hour). Patients were otherwise treated similarly, according to ADA guidelines. After resolution of DKA, patients treated with regular insulin received subcutaneous NPH and regular insulin twice daily, whereas patients treated with IV glulisine insulin received glargine once daily and glulisine before meals.

There were no differences in treatment outcome between the two groups. Due to cost considerations, there are no reasons to use rapid-acting analogs in IV insulin therapy.

- Alternatives to the intravenous route for insulin treatment — Patients with mild DKA can be safely treated with subcutaneous, rapid-acting insulin analogs .

Direct comparison of intramuscular, subcutaneous, and IV insulin therapy, for hemodynamically stable DKA patients, shows similar efficacy and safety[140-142]. In addition, subcutaneous administration of rapid-acting insulin analogs (insulin lispro, aspart, and glulisine) in the management of uncomplicated DKA has been demonstrated to be safe and cost effective in two randomized trials in adults[141,142].

iv) Bicarbonate and metabolic acidosis — The bicarbonate (HCO_3) can be administered if the arterial pH is less than 6.90 ; 100 mEq of sodium bicarbonate in 400 mL sterile water with 20 mEq of KCl, if the serum potassium is less than 5.3 mEq/L, administered over two hours.

The venous pH and bicarbonate concentration should be monitored every two hours, and bicarbonate doses can be repeated until the pH rises above 7.00. When the bicarbonate concentration increases, the serum potassium may fall, and more aggressive KCl replacement may be required.

Bicarbonate administration can cause several potential harmful effects:

- If bicarbonate infusion successfully increases the blood bicarbonate concentration, this can reduce the hyperventilatory drive, which will raise the blood pCO_2[143].
- The administration of alkali may slow the rate of recovery of the ketosis[144,145].
- Alkali administration can lead to a posttreatment metabolic alkalosis.)

The selected patients who may benefit from cautious alkali therapy[143] include:

- Patients with an arterial pH ≤6.9 in whom decreased cardiac contractility and vasodilatation can impair tissue perfusion.[146,147]
- Patients with potentially life-threatening hyperkalemia, since bicarbonate administration in acidemic patients may drive potassium into cells, and lowers the serum potassium concentration.[148]

v) Phosphate depletion — Phosphate replacement is not advised in the treatment of DKA or HHS. However, phosphate replacement should be strongly considered if severe hypophosphatemia occurs (serum phosphate concentration below 1.0 mg/dL or 0.32 mmol/L), especially if cardiac dysfunction, hemolytic anemia, and/or respiratory depression develop,[149-153] when potassium or sodium phosphate 20 to 30 mEq can be added to 1 L of IV fluid.

As phosphate replacement may have adverse effects, such as hypocalcemia and hypomagnesemia,[154-157]routine replacement is not indicated.

MONITORING

General — The serum glucose should initially be measured every hour until stable, while serum electrolytes, blood urea nitrogen (BUN), creatinine, and venous pH (for DKA) should be measured every two to four hours, depending upon disease severity and the clinical response.[3,158] The effective plasma osmolality (Posm) can be estimated from the sodium and glucose concentrations.

Repeat arterial blood gases are unnecessary during the treatment of DKA; venous pH, which is approximately 0.03 units lower than arterial pH,[159] is adequate to assess the response to therapy and avoids the pain and potential complications associated with repeated arterial punctures. If blood chemistry results are promptly available, an alternative to monitoring venous pH is to monitor the serum bicarbonate concentration (to assess correction of the

metabolic acidosis) and the serum anion gap (to assess correction of the ketoacidemia).

Resolution of ketoacidosis in DKA — The hyperglycemic crisis is considered to be resolved when the following goals are reached:

- The ketoacidosis has resolved, as evidenced by normalization of the serum anion gap (less than 12 mEq/L) and blood beta-hydroxybutyrate levels
- Patients with HHS are mentally alert and the plasma effective osmolality has fallen below 315 mOsmol/kg
- The patient is able to eat

In the absence of severe kidney disease, almost all patients develop a normal anion gap acidosis ("non-gap" or "hyperchloremic acidosis") during the resolution phase of the ketoacidosis. The hyperchloremic acidosis will slowly resolve as the kidneys excrete ammonium chloride (NH_4Cl) and regenerate bicarbonate.

Converting to subcutaneous insulin — The multiple-dose, subcutaneous insulin schedule is initiated h when the ketoacidosis has resolved and the patient is able to eat.

For patients with HHS, IV insulin infusion can be tapered and a multiple-dose, subcutaneous insulin schedule started when the serum glucose falls below 250 to 300 mg/dL (13.9 to 16.7 mmol/L).

The American Diabetes Association (ADA) guidelines for DKA recommend that IV insulin infusion be tapered and a multiple-dose, subcutaneous insulin schedule be started when the blood glucose is <200 mg/dL (11.1 mmol/L) and at least two of the following goals are met:[3]

- Serum anion gap <12 mEq/L (or at the upper limit of normal for the local laboratory)
- Serum bicarbonate ≥15 mEq/L
- Venous pH >7.30

The IV insulin infusion should be continued for one to two hours after initiating the subcutaneous insulin because abrupt discontinuation of IV insulin acutely reduces insulin levels and may result in recurrence of hyperglycemia and/or ketoacidosis. If the patient is unable to eat, it is preferable to continue the IV insulin infusion

For patients with known diabetes who were previously being treated with insulin, their pre-DKA or pre-HHS insulin regimen may be restarted. In insulin-naive patients, a multidose insulin regimen should be started at a dose of 0.5 to 0.8 units/kg per day, including bolus and basal insulin until an optimal dose is established.

COMPLICATIONS OF DKA—

Hypoglycemia and hypokalemia are the most common complications of the treatment of DKA and HHS. These complications have become much less common since low-dose insulin regimens and careful monitoring of serum potassium have been implemented.[160] Hyperglycemia may recur from interruption or discontinuation of intravenous (IV) insulin without adequate coverage with subcutaneous insulin.

Cerebral edema — Cerebral edema in uncontrolled diabetes mellitus is primarily a disease of children, and almost all affected patients are younger than 20 years old.[162] Symptoms typically emerge within 12 to 24 hours of the initiation of treatment for DKA but may exist prior to the onset of therapy.

Headache is the earliest clinical manifestation, followed by lethargy and decreased arousal. Neurologic deterioration may be rapid. Seizures, incontinence, pupillary changes, bradycardia, and respiratory arrest can develop. Symptoms progress if brainstem herniation occurs, and the rate of progression may be so rapid that clinically recognizable papilledema does not develop.

DKA-associated cerebral edema has a mortality rate of 20 to 40 percent.[3] Thus, careful monitoring for changes in mental or neurologic status that would permit early identification and therapy of cerebral edema is essential.

The 2009 American Diabetes Association (ADA) guidelines on hyperglycemic crises in diabetes in adults suggested that the following preventive measures may reduce the risk of cerebral edema in high-risk patients:[3]

- Gradual replacement of sodium and water deficits in patients who are hyperosmolar. The usual IV fluid regimen during the first few hours of treatment is isotonic saline at a rate of 15 to 20 mL/kg lean body weight per hour (approximately 1000 mL/hour in an average-sized person) with a maximum of <50 mL/kg in the first two to three hours.
- Dextrose should be added to the saline solution once the serum glucose levels have fallen to 200 mg/dL (11.1 mmol/L) in DKA or 250 to 300 mg/dL (13.9 to 16.7 mmol/L) in HHS. In patients with HHS, the serum glucose should be maintained at 250 to 300 mg/dL (13.9 to 16.7 mmol/L) until the hyperosmolality and mental status improve and the patient is clinically stable.

Case reports and small series in children suggest benefit from prompt administration of mannitol (0.25 to 1.0 g/kg) and perhaps from hypertonic (3 percent) saline (5 to 10 mL/kg over 30 min)[161]. These interventions raise the plasma osmolality (Posm) and generate an osmotic movement of water out of brain cells and a reduction in cerebral edema.

Noncardiogenic pulmonary edema — Hypoxemia and rarely noncardiogenic pulmonary edema can complicate the treatment of DKA[162-164]. Hypoxemia is attributed to a reduction in colloid osmotic pressure that results in increased lung water content and decreased lung compliance[11]. Patients with DKA who are found to have a wide alveolar-arterial oxygen gradient and /or rales may be at higher risk for the development of pulmonary edema.

III. AIMS AND OBJECTIVES

AIM OF THE STUDY

The study aims to find out various clinical and biochemical lab parameters that can predict the incidence and affect the outcome in diabetic ketoacidosis patients.

OBJECTIVES

- To find out if demographic parameters such as age, sex ,literacy , employment status and location of residence affect the incidence and outcome in diabetic ketoacidosis patients .
- To find out if the type of diabetes, duration of diabetes , treatment , previous history of diabetic ketoacidosis affect the incidence and outcome in diabetic ketoacidosis .
- To find out if alcohol intake, smoking , and comorbid illness affect the outcome in diabetic ketoacidosis patients .
- To find out if there is association between body mass index and incidence of diabetic ketoacidosis .
- To find out if the initial clinical presentation, Glasgow coma scale and precipitating factor affect the outcome in diabetic ketoacidosis .
- To find out the average HbA1c levels in patients presenting with diabetic ketoacidosis .

- To find out if the early electrolyte levels of sodium, potassium, chloride, magnesium, calcium , phosphorous at presentation affect the outcome in diabetic ketoacidosis .
- To find out if the initial renal parameters during presentation affect the outcome in diabetic ketoacidosis patients .
- To find out if the lipid profile affect the incidence and the outcome in diabetic ketoacidosis patients.
- To find out if the haemoglobin and total leucocyte count affect the incidence and the outcome in diabetic ketoacidosis patients .
- To find out if there is association between liver enzymes and outcome in diabetic ketoacidosis.
- To find out if there is association between albumin levels in the incidence and outcome in diabetic ketoacidosis .

IV .MATERIALS AND METHODS

a. Study design

This is a single centre prospective study. In this study, demographic , clinical and laboratory details were studied in patients presenting with diabetic ketoacidosis satisfying the study population criteria and the impact on the outcome was assessed .

b. Study centre

This study was conducted in the Department of General Medicine , Thanjavur Medical College and Hospitals, a government - run tertiary care centre located in the Cauvery Delta regions of Tamil Nadu .

c. Study period

The study was conducted from October 2016 to March 2017.

d. Study oversight

This study has been given ethical committee clearance by the local organization functioning in the tertiary care study centre.

e. Study population

Inclusion criteria

Group 1: Patients who were admitted in the study centre with age greater than 13 years and who were diagnosed to have diabetic ketoacidosis at the time of admission based on the following criteria: serum glucose >13.9 mmol/L (>250 mg/dL, enzymatic method), serum bicarbonate concentration <18 mmol/L, arterial pH <7.30 (selective ion exchange method), and ketonemia (3 mmol/L) and overt or significant ketonuria (more than 2+ on standard urine sticks). Informed consent was obtained from the patients and/or the closest relative.

Group 2:

Patients attending the diabetic outpatient department for monthly medications, who do not have previous episodes of DKA and who gave consent for the study.

Exclusion criteria

Patients who fulfilled the above criteria but excluded from the study were postcardiopulmonary resuscitated patients, late stages of chronic kidney disease, severe left ventricular dysfunction, terminal stages of cancer, decompensated liver disease, other ketotic states such as alcoholic ketosis and starvation ketosis ,lactic acidosis, hyperchloremic acidosis , drug or toxin induced acidosis and patients who did not consent .

f. Clinical assessment and demographic details:

Group 1: The initial clinical details on arrival at emergency department which included symptoms at presentation, vital signs, neurological status were assessed based on Glasgow coma scale(GCS) and other specific system findings were collected from the case records.

Then after establishment of diagnosis of diabetic ketoacidosis demographic history and thorough clinical details were collected from the patient and /or the closest relative.

Group 2: The demographic details and clinical details were obtained from the DM patients.

The demographic details consist of age, sex, literacy, occupation and residency of the patient.

The clinical history consists of time period of diagnosis of diabetes mellitus (DM), type of DM (was assessed with previous medical records and C peptide levels) ,treatment history , previous history of diabetic ketoacidosis, pre-existing comorbid illness, smoking & alcohol habits and specific histories related to suspected precipitating factors .

The BMI was calculated using the standard formula, weight (kg) / height (m^2). Height was measured using a standard stadiometer with the subjects standing in erect posture. The readings were taken to the nearest 0.1 cm. Weight was measured using a calibrated weighing machine with a beam balance.

g. Laboratory assessment

Group 1 (DKA patients): After the initial clinical assessment, blood investigations were taken, which included random blood sugar (RBS), serum electrolytes , renal function tests (RFT) , liver function tests (LFT) , plasma acetone , arterial blood gas analysis (ABG) , complete blood count (CBC) . In addition to lipid profile, glycated haemoglobin (HbA1c), urine routine examination and urine acetone were done for all patients included in the study.

Other additional investigations which were done included serum amylase, serum lipase, C-Reactive protein (CRP), chest x-ray, blood culture and sensitivity and urine culture and sensitivity based on individual patient requirements .

Group 2: The blood investigations done in these patients were random blood sugar (RBS), serum electrolytes, renal function tests (RFT), liver function tests (LFT) , plasma acetone , arterial blood gas analysis (ABG) , complete blood count (CBC), lipid profile and glycated haemoglobin (HbA1c) .

Normal values and method of measurement of individual parameters are given below :

TABLE 2: LAB PARAMETERS

Lab parameters	Normal range	Method used
Random blood sugar	70-100mg/dl	Glucose oxidase – tinder's method
Ph	7.34-7.43	Arterial blood gas analyser
HCO3	24-26 mmol/l	Arterial blood gas analyser
Sodium	136-146 meq/l	Ion selective electrode technology
Potassium	3.5-5 meq/l	Ion selective electrode technology
chloride	102-109mg/dl	Ion selective electrode technology
magnesium	1.5-2.3 mg/dl	Colourimetry method
phosphorous	2.5-4.3mg/dl	Ammonium molybdate method in coulter analyser
Total calcium	8.7 -10.2 mg/dl	o-cresolphthalein complexone method
blood urea	20-40 mg/dl	Enzymatic berthelot method
blood urea nitrogen (bun)	7-20mg/dl	Urea/2.14
serum creatinine	female – 0.5-0.9 mg/dl male – 0.6-1.2 mg/dl	Jaffe's method
HbA1c	<6.5g%	Immunoturbidometry method
<u>Lipid profile</u> HDL LDL VLDL TC TGL	 40-50 mg/dL(males) 50-60 mg/dL(females) 100-129 mg/dL 2-30 mg/dL <100 mg/dL 101-150 mg/dL	 Immunoinhibition Friedwald's formula -TC-(HDL-C+VLDL-C) TGL/5 Cholesterol esterase-Cholesterol oxidase Enzymatic Colorimetric method

LFT AST ALP ALP TB TP Albumin	 5-40 IU/L 5-35 IU/L 35-130 IU/L 5-17 µmol/L 6.7-8.6 g/dl 4-5g/dl	Specific reagents were used and analysed using Beckman Coulter Bromocresol blue
Serum osmolality	285-295 mosm/l	2(Na+K) +BUN/2.8+glucose/18
Hemoglobin	12 -16 g/dl	SYSMEX automated cell counter
TLC	4000 -9000 cells /mm3	SYSMEX automated cell counter

h. Follow up and outcome:

Group 1: The patients diagnosed with DKA were managed with fluids, regular intravenous insulin, potassium supplementation were monitored regularly and followed up until they were discharged from the hospital. The primary outcome assessed in this group was death.

Group 2: These groups of patients were reviewed after 1month period in the diabetic out patient department. Patients who have had change in medications in that 1 month, those who have had episodes of DKA and who did not return for review were excluded from the study.

i. STATISTICAL ANALYSIS:

Data was entered into Microsoft Excel. Statistical analysis was done using software Graph Pad Prism Version 5 and SPSS-version 24. Data were expressed as mean with standard deviation. Categorical values were reported using number and percentage and compared using Fischer's exact test. Odd's ratio was calculated for predictors of final outcome. Sensitivity and specificity were calculated that can be used as predictors of outcome. Probability value (p valve) less than 0.05 was considered as statistically significant.

V-RESULTS

Group 1 (DKA): A total of 42 patients studied were recruited in the study, in which 30 of them were included in the study based on the defined study criteria. Out of the 30 patients, 22 patients were discharged and 8 patients succumbed to death.

Group 2 (Non ketotic DM): A total of 56 patients were recruited for the study, in which only 35 of them were included in the study . Other 21 were excluded as they didn't meet the study criteria, some did not review in the following month and others had a change in medications.

1.Demographic characteristics

a) Age distribution

Group 1: The age of the study subjects ranged from 15years to 75 years, with mean age 41±17.08. Most of the deaths were in the age group greater than 40, but was not statistically significant (p= 0.266).

TABLE 3: Age distribution in group 1-(i)

Age (years)	Group 1 n (%)	Discharged n	Death N
13-19	3 (10%)	3	0
20-39	11 (37%)	9	2
40-59	10 (33%)	5	5
>60	6 (20%)	5	1

FIGURE 2 : Outcome Distribution Based On Age

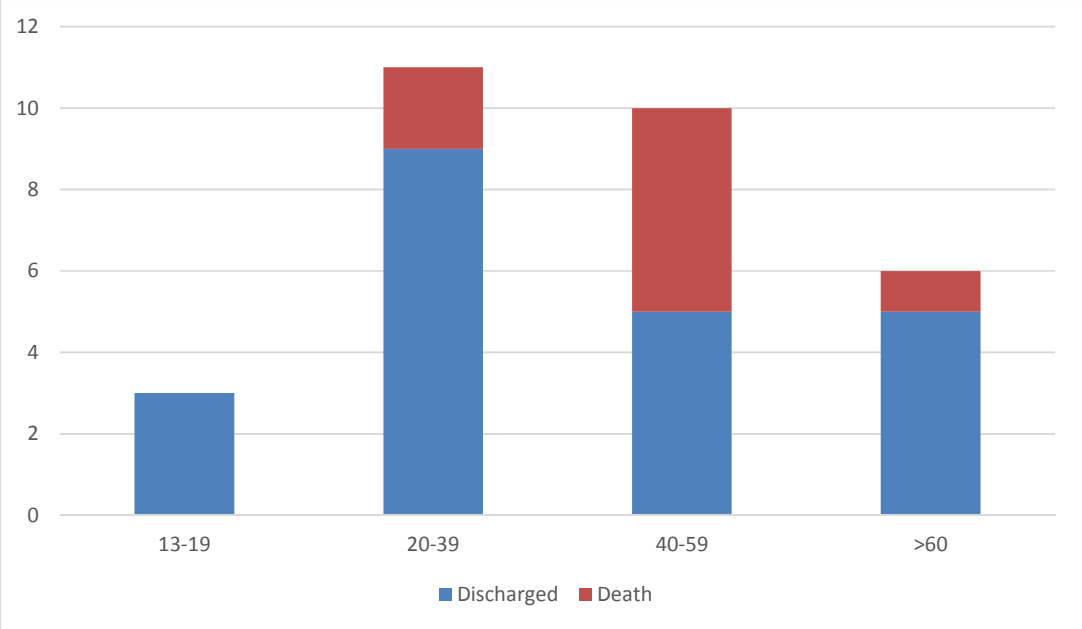


TABLE 4: Age distribution in group 1-(ii)

Age(years)	Total-n	Discharged-n	Death-n	P value
<40	14	12	2	0.266
>40	16	10	6	

Group 2: The majority of the population studied were greater than 40 years, with mean age being 56.36±10.36.

Comparison of group 1 and 2: In comparing both the age groups, the incidence of DKA was more common in age group lesser than 40 years, and was statistically significant with p value of 0.0001.

TABLE 5: Comparison of age distribution in group 1 and 2-(i)

Age (years)	Group 1-n(%)	Group 2-n(%)
13-19	3(10)	0(0)
20-39	11(37)	1(2.8%)
40-59	10(33)	19(54%)
>60	6(20)	15(42.85%)

TABLE 6: Comparison of age distribution in group 1 and 2-(ii)

Age (years)	Group 1-n	Group 2-n	P value
<40	14	1	.0001
>40	16	34	

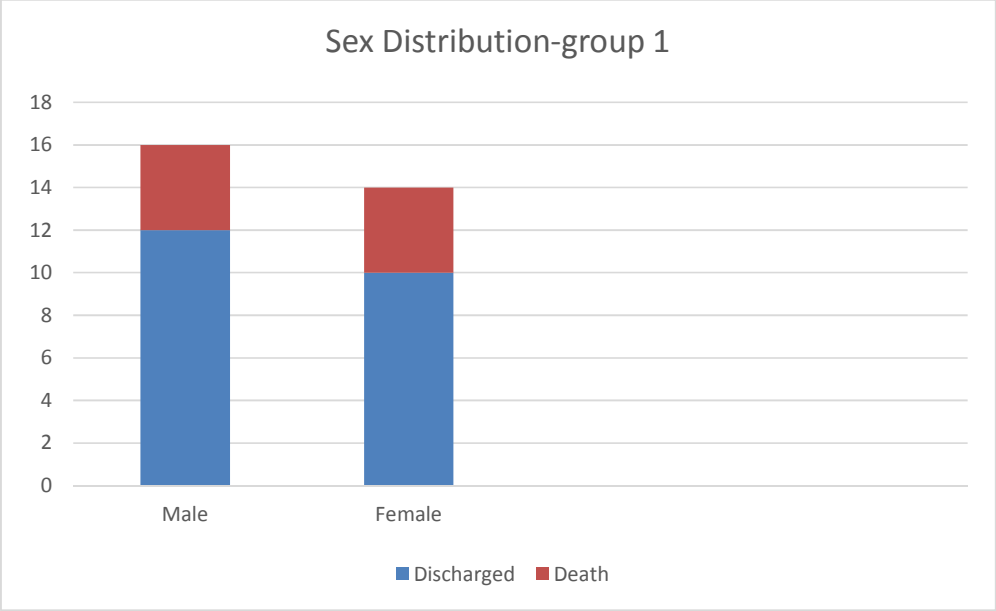
b) Sex distribution

Group 1: Most of the patients were males (53%) and outcome was not dependent on the sex of the patient statistically (p=0.825).

TABLE 7: Sex distribution in group 1

Sex	Total population-n (%)	Discharge-n (%)	Death-n (%)	P value
Male	16 (53%)	12(40%)	4(13.33%)	0.825
Female	14 (47%)	10(33.33%)	4(13.33%)	

FIGURE 3 : Sex distribution in DKA group



Comparison of group 1 and 2: The sex of the patient does not affect the incidence of DKA in the study population (p=0.4605).

TABLE 8: Comparison of sex distribution in group 1 and 2

Sex	Group 1- n (%)	Group 2 -n (%)	P value
Male	16(53%)	15(42%)	0.4605
Female	14(46%)	20(57%)	

c) Distance of residence from tertiary care centre

Group 1: The distance away from the hospital did affect the outcome in DKA patients with no deaths in the group within 10 km of hospital reach (p=0.02)

TABLE 9: Distribution of Distance of residence from tertiary care centre

Distance away from hospital	Total population n	Discharged n	Death n
<10km	18	10	0
11-40 km	8	4	4
>40 km	12	8	4

d) Employment status – Most of the study population falls in to the labour group and no professionals, as the study tertiary care hospital is located centring rural areas.80% and 68% of the study population were employed in group 1 and 2 respectively.

TABLE 10: Employment status in study population-(i)

Occupation	Group 1			Group 2
	Total population n	Discharge n	Death n	
Professional	0	0	0	0
Farmer	5	2	1	3
Skilled worker	10	9	3	3
Unskilled worker	5	4	1	18
Unemployed	7	4	3	11
Student	3	3	-	-

TABLE 11: Employment status in study population-(ii)

Employment status	Group 1				Group 2 n%	P value
	Total population n%	Discharge N	Death n	P value		
Employed & studentship	24(80%)	19	5	0.3	24(68.57%)	0.3984
Unemployed	6(20%)	3	3		11(31.42%)	

e) Educational qualification – About 30% of population in group1 and 28.5% in group 2 are illiterates.

TABLE 12: Educational qualification in study population

Education	Group -1			Group -2
	Total population-n%	Discharge n%	Death n%	n%
Illiterate	9(30%)	6	3	10(28.5%)
Primary	6(20%)	3	3	9(25%)
High school	13(43%)	11	2	16(45.7%)
Diploma/Graduate	2(6%)	2	0	0(0%)

f) Type of DM – In patients with DKA, 56.66% of them belonged to T2DM. TIDM patients had favourable outcome compared to non T1DM group

(p =0.028).

TABLE 13: Distribution of Type of DM in study population

Type of diabetes	Group 1			Group 2 N
	Total population n	Discharge n	Death n	
Type 1	10 (33.33%)	10	0	1(2%)
Type 2	17(56.66%)	11	5	34(97%)
Others(exocrine pancreas)	3(10%)	1	2	-
Did not classify	1(3%)	0	1	-

TABLE 14: Association of T1DM with outcome in DKA

T1DM	Total population	Discharge	Death	P value
YES	10(33.33%)	10(45.45%)	0(0%)	0.0288
NO	20(66.66%)	12(54.54%)	8(100%)	

TABLE 15: Association of T2DM with outcome in DKA

T2DM	Total population	Discharge	Death	P value
YES	17(56.66%)	11(50%)	5(6.25%)	0.6887
NO	13(43.33%	11(50%)	3(37.5%)	

g) Treatment of DM- In the DKA population 76% of them were known cases of DM and have be advised treatment ; and it did not affect the outcome.

TABLE 16: Treatment history of DM population in the study

Treatment	Group 1(n)	Group 2(n)
Insulin	7	5
OHA	15	30
OHA &Insulin	1	-
Nil	7	-

TABLE 17: Association between outcome and new DM in DKA

History of treatment	Total population-n%	Discharge n%	Death n%	P value
Yes	23(76%)	18(81.81%)	5(62.5%)	0.3446
No (new DM)	7(23.33%)	4(18.18%)	3(37.5%)	

h) Previous DKA episodes –The history of previous episodes of DKA did not significantly affect outcome in DKA population(p=0.28).

TABLE 18: Association between previous DKA episodes and outcome

Previous DKA episode	Total population	Discharge	Death	P value
No	25(83.33%)	17(77.27%)	8(100%)	0.2868
Yes	5(16.66%)	5(22.72%)	0(0%)	

i) Alcohol and smoking habits – did not influence the outcome in DKA

TABLE 19: Alcohol and smoking habits in study population

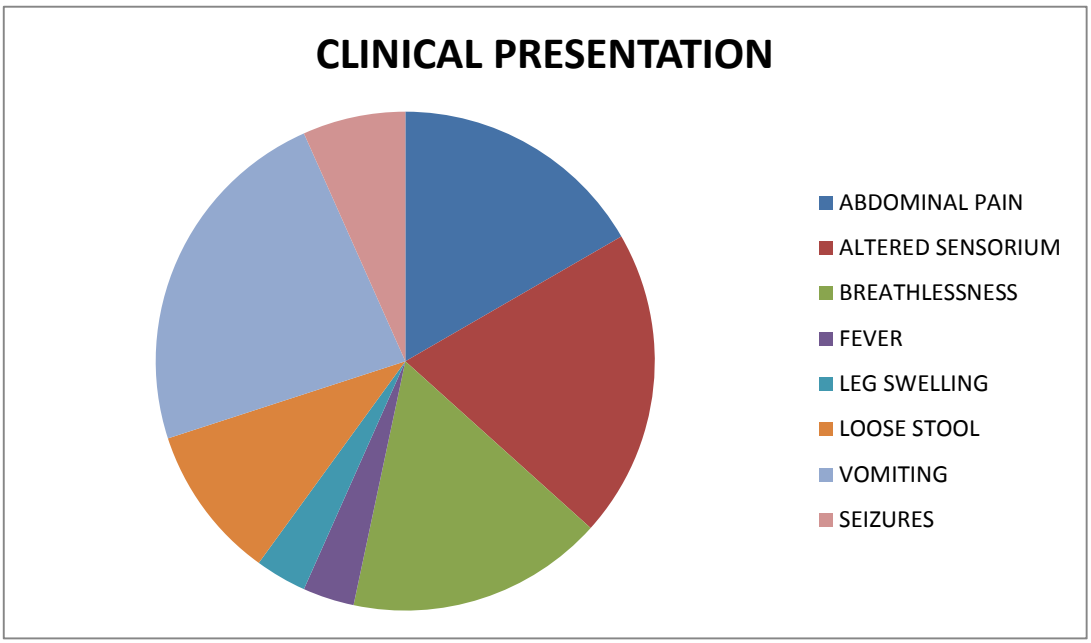
Addiction	Group 1	Group 2
Alcohol	5	6
Smoking	2	6

j) Clinical presentation of DKA- The most common presentation with in the population studied was vomiting(23%) and then altered sensorium(20%).

Table 20 – Clinical presentation in DKA population

Clinical presentation	Total population	Discharge	Death
Abdominal pain	5(17%)	3	2
Altered sensorium	6(20%)	3	3
Breathlessness	5(17%)	5	0
Fever, weight loss	1(3%)	1	0
Leg swelling	1(3%)	1	0
Loose stool	3(10%)	3	0
Vomiting	7(23%)	5	2
Seizures	2(7%)	2	0

FIGURE 4: Clinical presentation in DKA population



k) GCS during presentation of DKA patients – In this study low GCS score at presentation has been linked to poor outcome in DKA.

TABLE 21: GCS during presentation of DKA patients-(i)

GCS	Total population	Discharge	Death
<8	6	0	6
8-12	5	5	0
>13	19	17	2

TABLE 22: GCS during presentation of DKA patients-(ii)

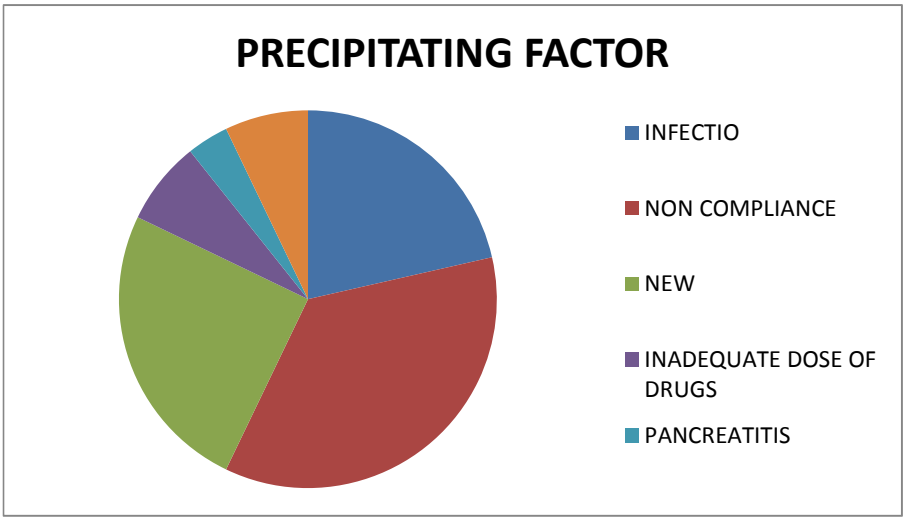
GCS	Total population	Discharge	Death	P VALUE
<9	6	0	6	0.0001
>9	24	22	2	

l) Precipitating Factor – The most common precipitating factor was newly diagnosed DM (25%) followed by infection(21%).

TABLE 23: Precipitating factors in DKA population

PRECIPITATING FACTORS	Total population	Discharged	Death
Infection	6(21%)	4	2
Non-compliance	10(36%)	7	3
New	7(25%)	5	2
Inadequate dose	2(7%)	2	0
Not known	2(7%)	2	0
Pancreatitis	1(4%)	1	0

FIGURE 4: Precipitating factors in DKA



m) BMI distribution – Most of the population in the DKA group (63.33%) were undernourished vs 8% in non ketotic group ; and was statistically significant.

TABLE 24 : Categorical comparison of BMI

BMI	GROUP 1	GROUP 2	P value
<18.5	19(63.33%)	3(8%)	0.0001
>/=18.5	3(10%)	32(91.4%)	

TABLE 25: Comparison of BMI in group 1 and 2

BMI	GROUP 1	GROUP 2
Underweight(<18.5)	19	3
Normal(18.5-25)	3	23
Overweight(25.1-30)	-	5
Obesity(30.1-40)	-	3
Morbid obesity(>40)	-	1

n) Biochemical profile in DKA patients- The biochemical parameters that were statistically ($p<0.05$) found to affect the outcome were serum osmolality , renal parameters and total calcium.

TABLE 26: Categorical comparison of RBS values

RBS	Total population	Death	Discharge	P value
<500	16	3	13	0.4171
>500	14	5	9	

TABLE 27: pH values of study population

pH	Total population	Discharge	Death
<7.1	12(45%)	8	4
7.1 -7.2	13(49%)	13	0
>7.25	5 (6%)	1	4

TABLE 28: Parameters evaluated to find the influence on outcome

Parameter	DISCHARGED		DEATH		P value	Confidence interval
	Mean	SD	Mean	SD		
Sodium(meq/l)	145.164	7.921	148.613	9.571	0.3265	-10.522 to 3.624
Potassium (meq/l)	4.414	0.854	4.525	1.260	0.7833	-0.933 to 0.710
Chloride (meq/l)	93.09	12.75	89.50	7.09	0.4595	-6.22 to 13.40
Magnesium (meq/l)	2.745	1.1144	3.037	1.392	0.5638	-1.316 to 0.732
Phosphorous (mg/dl)	2.914	0.993	4.2	2.712	0.0625	-2.645 to 0.072
Total calcium (mg/dl)	8.455	1.448	6.550	1.404	0.0033*	0.689 to 3.120
Serum osmolality	308.41	17.32	325	22.14	0.0399*	-32.36 to -0.82
Blood urea (mg/dl)	41.77	17.07	98.25	33.64	0.0001*	-75.42 to -37.54
BUN (mg/dl)	19.4041	8.0570	45.8525	15.7021	0.0001*	-35.3313 to -17.5655
Serum creatinine(mg/dl)	0.965	0.375	2.113	0.923	0.0001 *	-1.643 to -0.652
HDL (mg/dl)	30.82	12.14	28.38	11.60	0.6261	-7.71 to 12.60
LDL (mg/dl)	81.736	30.564	76.500	37.489	0.6987	-22.193 to 32.666
VLDL (mg/dl)	35.627	29.506	42.00	20.305	0.5790	-29.626 to 16.881

TC (mg/dl)	143.80	51.21	146.63	40.20	0.8903	-44.52 to 38.87
TGL (mg/dl)	185.68	156.55	204.38	105.84	0.7580	-141.78 to 104.39
SGOT (IU/l)	27.82	10.41	34.75	24.89	0.2839	-19.93 to 6.06
SGPT (IU/l)	23.77	9.14	22.75	10.70	0.7973	-7.06 to 9.10
TP (g/dl)	5.432	0.619	5.900	0.621	0.0779	-0.992 to 0.056
Serum albumin (g/dl)	2.423	0.671	2.900	0.758	0.1068	-1.064 to 0.109
Hb (g%)	10.918	1.631	9.850	1.235	0.1043	-0.235 to 2.372
TLC (cells/mm^3)	8268.18	5268.18	12475.00	5681.74	0.0683	-8752.12 to 338.48
HbA1c %	12.809	2.125	13.588	0.775	0.3247	-2.369 to 0.812

* indicates $p<0.05$ and considered statistically significant.

o) Predictors of outcome in DKA – T1DM, GCS, total calcium, blood urea, serum creatinine at the initial presentation influenced the outcome in DKA.

TABLE 29: Comparison of variables influencing death in DKA

S. No	Parameter		Death (n=8)		Discharge (n=22)		P Value	Odds ratio (95% CI)
			N	%	n	%		
1	Total calcium (mg/dl)	<8.5	7	87.5	5	22.7	0.0025*	23.8(2.4 to 279)
		>8.5	1	12.5	17	77.3		
2	Serum osmolality (mosm/l)	>310	6	75	10	45	0.22(NS)	---
		<310	2	25	12	55		
3	Blood urea (mg/dl)	>40	7	87.5	8	36.4	.035*	12.25(1.4 TO 146)
		<40	1	12.5	14	63.6		
4	Serum creatinine (mg/dl)	>1.2	7	87.5	5	23	.002*	23.8(2.4 to 279)
		<1.2	1	12.5	17	77		
5	GCS	<9	6	75	3	14	0.003*	19(2.3 to109)
		>9	2	25	19	86		

Data are expressed as absolute numbers with proportions. Fisher's exact test was used to test the difference between the proportions. * indicates $p<0.05$ and considered statistically significant.

p) Predictors of DKA in DM population -The following parameter in table-30 were analysed and found that there is significant variation in parameter values such as serum potassium , lipids , AST, ALT and renal parameters which wee acutely affected by ketosis . The other parameters which were not acutely affected but showing significant variability were total protein, serum albumin , HbA1c and BMI. The sensitivity and specificity of each of these parameters were tested (table -32)

TABLE 30: Parameters analysed to be used as predictors of DKA

Parameter	GROUP 1 -DKA		GROUP 2- DM without ketosis		P value	Confidence interval
	Mean	SD	Mean	SD		
Sodium(meq/l)	146.083	8.363	144.057	8.363	0.2538	-1.490 to 5.542
Potassium (meq/l)	4.443	0.956	4.034	0.616	0.0417*	0.016 to 0.802
Chloride (meq/l)	92.55	11.48	88.26	17.51	0.2613	-3.28 to 11.87
Magnesium (mg/dl)	2.756	1.184	2.270	0.914	0.0671	-0.0351 to 1.0068
Phosphorous (mg/dl)	3.256	1.680	3.891	0.935	0.0598	-1.2970 to 0.0269
Total calcium (mg/dl)	7.947	1.652	8.631	0.501	0.0228 *	-1.271 to -0.098
Blood urea (mg/dl)	56.83	33.61	38.51	14.55	0.0048 *	5.80 to 30.84

Serum creatinine (mg/dl)	1.221	0.737	0.889	0.428	0.0281*	0.037 to 0.627
HDL (mg/dl)	30.17	11.85	39.20	10.32	0.0017 *	-14.53 to -3.54
LDL (mg/dl)	80.340	31.957	109.371	32.949	0.0006 *	-45.189 to -12.874
VLDL (mg/dl)	36.743	27.192	37.171	18.897	0.9415	-12.060 to 11.203
TC (mg/dl)	146.97	46.86	178.14	39.31	0.0049 *	-52.53 to -9.82
TGL (mg/dl)	188	144	183.74	90.87	0.8867	-55.26 to 63.77
SGOT (IU/l)	29.67	15.42	11.51	4.88	0.0001 *	12.65 to 23.65
SGPT (IU/l)	23.50	9.40	8.71	3.63	0.0001 *	11.35 to 18.22
TP (g/dl)	5.566	0.654	7.300	0.619	0.0001*	-2.053 to -1.416
Serum albumin (g/dl)	2.562	0.724	3.717	0.480	0.0001 *	-1.458 to -0.852
Hb (g%)	10.633	1.589	11.814	1.754	0.0063 *	-2.016 to -0.346
TLC (cells/mm^3)	9390	5609.80	6960.00	2091.33	0.0204 *	389.27 to 4470.73
HbA1c %	13.017	1.881	8.231	2.275	0.0001 *	3.740 to 5.831
BMI	16.947	1.253	23.708	5.0955	0.0001 *	-8.9857 to -4.5360

TABLE 31: Comparison of parameters found to be significantly affected in DKA

S. No	Parameter		DKA (n=30)		DM -no ketosis (n=65)		P Value	Odds ratio (95% CI)
			N	%	n	%		
1	Potassium	>4.5	9	30	13	37	0.6(NS)	-
		<4.5	21	70	22	63		
2	Total calcium(mg/dl)	<8.5	13	43	9	26	0.19(NS)	
		>8.5	17	57	26	74		
3	Blood urea (mg/dl)	>40	16	53	7	20	0.008*	4.8(1.44 to13)
		<40	14	47	28	80		
4	Serum creatinine(mg/dl)	>1.2	12	40	6	17	0.053 (NS)	
		<1.2	18	60	29	83		
5	Total protein(g/dl)	<6	21	70	1	3	<0.0001	81.7(11.7-865)
		>6	9	30	34	97		
6	Serum albumin(g/dl)	<3.5	28	93	13	37	<0.0001	23.7(4.9 to 108)
		>3.5	2	7	22	63		
7	Hemoglobin (g%)	<11	16	53	9	26	.0039	3.3(1.1 to 9.8)
		>11	14	47	26	74		
8	HbA1c	>10	29	97	9	26	<0.0001	83.7 (12 to 885)
		<10	1	3	26	74		

* indicates p<0.05 and considered statistically significant.

TABLE 32: Diagnostic test values of covariates that can be used to predict DKA in population

S. No	Variables (if positive)	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
1	Total protein	70	97.2	95.5	79.6
2	Serum albumin	93.3	62.9	68.3	91.7
3	Hemoglobin	53.3	74.3	64	65
4	HbA1c	96.7	74.3	76.3	96.3
5	BMI	86.4	91.4	86.4	91.4

VI-DISCUSSION

In total of 30 DKA patients studied 28% of them had unfavourable outcome. This was near similar to the studies conducted by Oschatz et al.[165] and Agarwal A et al.[9] who showed 29% and 30% mortality in their study in DKA patients. The mortality is rarely due to metabolic complications and is mostly due to underlying precipitating illness. [166,167]

In developed countries adult subjects with DKA have overall mortality <1% ;[5] however, a mortality rate >5% has been reported in the elderly and in patients with concomitant life-threatening illnesses.[168,169]

In developing countries, one reason could be lack of adequate medical facility and late referrals. In this study major population succumbed to death were residing at a distance greater than 10 km from the tertiary care centre (p=0.02).

The deaths in study population showed that the individuals who died had, one or other of the accompanied co-morbid illness,or complicated precipitating factors , which were, substance abuse and schizophrenia ; fibrocalcific pancreas, pancreatitis ; serious sepsis ; rhinocerebral mucormycosis ;and stroke. So, the death in this group was not linked to direct metabolic complications.

In this present study, the median age of incidence of DKA was 41±17 years, with increased incidence in ages less than 40 years of age, and age was not found significant statistically, affecting the outcome. This was similar to results obtained by Agarwal et al who included a total of 270 patients in the study.[9] In international study published in ADA,[3]stated that most patients with DKA were between the ages of 18 and 44 years (56%) and 45 and 65 years (24%), with only 18% of patients <20 years of age;[3] and the prognosis of DKA is substantially worsened at the extremes of age. [11]

This study did not show any predilection in sex affecting the incidence and outcome in DKA. In international review, females have found to have increased incidence of DKA, whereas Agarwal A et al showed male gender had 7.93 fold more favourable outcome.[170]

It is stated in previous studies that two-thirds of diabetic patients presenting with DKA are T1DM [3]; and DKA related to T2DM has an intractable course and worst outcomes.[171]But in this study, majority of population presented with DKA were T2DM (56%) and T1DM patients showed better outcomes compared to T2DM. A similar result was produced by Adhikari et al., which showed 62.8% of DKA patients had T2DM compared to 37.8% with T1DM .[172]The reason for increased incidence of DKA in T2DM could be an indicator of

changing profile in T2DM due to influence of changing social and environmental factors in developing countries like India, which is required to be scrutinized .

DKA presents with various clinical manifestations . One such manifestation is altered sensorium which occurred in 20% of the study population and was the commonest manifestation following vomiting which occured in 26% of DKA population studied. The initial GCS calculated significantly affected the outcome. The worst outcomes were documented in individuals with less than 8 score. The previous studies did not show constant association of outcome with GCS. In study by Otieno et al.,[173] altered level of consciousness was a major predictor of mortality in DKA patients whereas Agarwal et al. dID not show such association.[9]

The hematological parameters were not significantly associated with outcome in DKA. There is generally, leucocytosis in DKA, when accompanied with infection counts are greater than 25,000cells/mm^3 and is associated with increased mortality.[174,175] In this study we had one patient with persistently higher than 20, 000 cells/mm^3, and she succumbed to death. No other patient had such high counts.

In the biochemical parameters studied, renal parameters i.e., blood urea and serum creatinine were the parameters associated with the worst outcome . The mean value of these parameters in the worst outcome group were

98.25mg/dl and 2.11mg/dl respectively. It is consistent with most studies which showed failure of renal function leads to death.[175] So, early recognition and adequate rehydration should be one of the major keys in management.

Our study did not show any major association between the electrolyte disturbances and death, except for serum calcium. Phosphate, magnesium and calcium are other elements with potassium, excreted in excess in urine during the development of DKA owing to osmotic diuresis, and a deficit of 1–2 mmol/kg on average occurs.[176,177]

Though many studies have shown association between phosphate and death,[9] this study did not show any significance.

Liver function tests and lipid profile at the time of admission did not affect the outcome. Though there are studies showing increased AST and ALT in patients with worst outcome,[9] which might be due to major hemodynamic imbalance.

The serum osmolality when assessed as continuous variable showed significant influence outcome but when categorised (310mosm/l-cutoff) did not affect outcome. Singi et al.[178] and Agarwal et al.[9] had showed, increased serum osmolality >320momol/l is linked with worst outcome.

The mean HbA1c values in DKA group with the worst outcome was 13.58±0.77 % vs better outcome which was about 12.8±2.12% ad was not statistically significant .

The DKA population was compared with the DM population without ketosis to find out the possible parameters that could predict the incidence of DKA. There were significant variability between the means of parameters analysed in two populations. Those showed significant variability were serum potassium levels, total calcium, renal parameters, HDL, LDL, and total cholesterol, AST, ALT, total protein, serum albumin, haemoglobin, TLC, HbA1c and BMI.

In which, the serum potassium, total calcium, renal parameters, lipid levels, AST, ALT are found to be acutely affected due to ketosis in DKA. Whereas serum albumin levels, total protein, HbA1c and BMI are affected by the insulin deficiency /insufficiency states.[179]

Insulin has varied effects on liver protein synthesis. It has been found in murine models that insulin is required for expression of albumin by inhibition of Forkhead Box O1 protein. Its insulin sufficiency rather than insulin resistance affects the albumin production.[187]In this study serum albumin <3.5g/dl and Total protein < 6g/dl had p value <0.0001 and had high sensitivity in predicting DKA in DM individuals.

DKA is associated with increased HbA1c levels which reflect both fasting and postprandial hyperglycemia[180] in T1DM[181-183] and T2DM[184].A mean cut of value of HbA1c > 10% was highly specific (pvalue<0.0001) to find out individuals prone for DKA.

Many studies have shown that lower BMI is associated with increased incidence of DKA.[185-186]There are also studies showing bimodal distribution of BMI affecting DKA in T2DM but not with T1DM . This study showed BMI < 18.5 was highly sensitive (p value< 0.0001) with sensitivity and specificity of about 86.4% and 91.4% respectively. So, further studies have to be done to characterize cut off values of BMI below or above which individuals are susceptible to DKA.

VII- CONCLUSION

DKA is treatable with better outcome, if identified early, and if kidney injury is prevented. This study throws light into the various predictors of DKA affecting its occurrence and outcome.

Key outcomes include:

Poor prognostic factors in DKA were kidney injury and complicated precipitating factors such as sepsis, pancreatitis and rhinocerebromucormyosis.

Serum albumin <3.5g/dl, HbA1c>10% and Body mass index <18.5% can be used as early predictors of DKA. Further studies should be done to standardize the levels of these parameters in association with occurrence of DKA.

VIII. STUDY LIMITATIONS

- This study contains small study group.
- It was conducted in a single centre hence there is chance for selection bias in the study.
- The study subjects were not followed up for long term period.
- Multivariate logistic regression analysis couldn't be used in this study to correlate the predictors because of small sample size.

IX. STUDY IMPLICATIONS

Clinical implications

- Diabetic ketoacidosis should be one among the first differential diagnoses to be considered in malnourished patients presenting with acidosis.
- Prevention or early identification of renal shutdown in patients with DKA can produce good outcome.
- Serum Albumin, Body mass index and HbA1c can be used as a powerful screening tools to detect individuals prone for DKA and take adequate measures earlier.
- Serum Albumin can predict the usefulness or need of insulin therapy in T2DM as serum albumin reflects the function of beta cells of pancreas.

CONSENT FORM

Dr. SHAARON S, Post Graduate Student in the Department of General Medicine, Thanjavur Medical college, Thanjavur is doing a work on "A STUDY OF "PREDICTORS AND FACTORS AFFECTING OUTCOME IN DIABETIC KETOAIDOSIS PATIENTS". The procedure has been explained to me clearly.

The procedure has been explained to me clearly. I understand that there is no risk involved in the above procedures. I hereby give my consent to participate in this study.

Signature

Name:

Place:

PREDICTORS AND FACTORS AFFECTING OUTCOME IN DKA PATIENTS

Name: Age: Sex: Address:

Occupation: Education:

DM diagnosed 1st :

Duration of **DM :**

No. of episodes of hospital admission for DKA:

Last episode of DKA:

Treatment of DM on treatment

OHA

Insulin

Change of dose in HA dose in recent past (last change)

BMI : wt: ht: WHR:

Comorbid illness :

Alcohol and Smoking habits :

Clinical features

@presentation	**Day**	**Day**	**Day**

Neurological status

@presentation	Day 1	Day 2	Day 3	Day 4	Day 5

Precipitating factor

Sepsis/ infection	Intercurrent illness
Non compatibility	Alcohol abuse
MI	Trauma
stroke	PE
Psychological status	Pancreatitis

Biochemical parameters

	1	2	3
RBS			
ABG - PH			
Hco3			
Pco2			
PO2			
Severity of DKA			

	@presentation	1	acetone -ve
Na+			
K+			
Cl-			
Mg+			
Phosphorus			
ca+			

HbA1C			

Blood urea			
Sr. Creatinine			

Cortisol			

Lipid profile			
HDL			
LDL			
VLDL			
TGL			

CBC:

HB%			
TC			
DC			
PCT			
PCV			

LFT			
SGOT			
SGPT			
S. Bilirubin -DB			
-IDB			
Total protein			
S. ALP			
Albumin			

Blood c/s :

Urine c/s :

ESR:

CRP:

ECG:

TREATMENT :

COMPLICATIONS :

OUTCOME:-

sl. No.	ip no.	age	sex	address	distance from hosptal	occupation	education	typE of DM	duration of dm	treatment	previous dka episodes	alcohol	smoking	comorbid illness	BMI
1	36912	25	f	thanjavur	10 km	unemployed	12th std	1	3 month	OHA	NIL	NO	NO	NO	17
2	29836	55	f	manargudi	40	housewife	illiterate	2	2 years	oha	nil	no	NO	no	17.2
3	26186	40	f	thanjavur	9	housewife	illiterate	2	2years	metformin,glimepride	1	no	no	no	17.8
4	24407	30	m	pattukottai	51	driver	10th	1	3 years	insulin	3	no	no	no	16.45
5	30187	33	m	kalvirayanpettai	22	farmer	diploma	pancreatitis	6 months	insulin	no	no	no	chronic pancreatiti	19
6	24447	27	m	valangai	38	unemplyed	12th std	1	6months	insulin	2	no	no	ptb defaulter	15.6
7	24433	61	m	ariyalur	45	farmer	illiterate	2	4 years	oha and insulin	1	no	no	ht	16.7
8	25418	38	m	kalavram	12	milk vendor	8th std	2	5 years	metformin	no	yes	no	no	16.8
9	25916	68	f	orthanadu	23	unemployed	5th std	2	3 years	oha	1	no	no	no	14.3
10	45400	20	m	thanjavur	5	hair stylist	12th std	1	new	no	no	no	no	no	16.2
11	45903	65	m	palliagaram	10	farmer	illiterate	2	5 years	oha	no	no	no	no	16.4
12	32969	67	f	thanjavur	9	unemployed	illiterate	2	5 years	oha	nil	no	NO	no	16
13	25927	55	f	ariyalur	45	housewife	primary	2	6 years	oha	nil	NO	no	PLWHA	16
14	28121	30	f	madhakovil	22	housewife	12th std	1	5 years	oha	nil	no	no	no	17
15	29481	52	m	thanjavur	10	painter	12th std	2	2years	oha	nil	yes	no	no	19.6
16	24431	16	m	thanjavur	9	11th std	11th std	1	new	no	nil	no	no	no	19
17	46121	17	f	pattukottai	51	12th std	12th std	1	new	no	nil	no	no	no	16
18	34833	15	f	thanjavur	8	9th std	9th std	1	1 year	insulin	nil	no	no	no	16.2

sl. No.	ip no.	age	sex	address	distance from hosptal	occupation	education	typE of DM	duration of dm	treatment	previous dka episodes	alcohol	smoking	comorbid illness	BMI
19	34600	65	m	thanjavur	6	farmer	12th std	2	5 years	insulin	nil	no	NO	no	17.8
20	35592	25	m	pattukottai	51	electrician	12thstd	1	new	no	nil	no	no	no	17.2
21	34904	36	m	pattukottai	51	employed	diploma	1	5years	insulin	nil	no	no	no	18.4
22	29303	40	f	thanjavur	7	housewife	illiterate	2	1 year	oha	nil	no	no	no	16.2
23	34637	33	m	thanjavur	8	unemployed	high school	?1	new	no	nil	yes	yes	schizophrenia /	
24	37195	27	m	pattukottai	51	unemployed	high school	fibrocalcific pancreas	3 months	insulin	nil	no	no	no	
25	30239	45	f	pattukottai	51	coolie	illiterate	2	5years	oha	nil	no	no	no	
26	31004	43	f	orathanadu	23	housewife	illiterate	2	2 years	oha	NIL	no	no	no	
27	45412	45	f	pattukottai	51	housewife	primary	2	6 years	oha	nil	no	no	stroke	20
28	35497	49	m	pattukottai	51	farmer	primary	2	2 weeks	oha	nil	yes	yes	no	17
29	25969	52	m	pudhukottai	26	unemployed	primary	pancreatitis	new	no	nil	yes	no	no	
30	45325	75	f	papanasam	25	housewife	illiterate	2	new	no	NIL	no	no	no	

sl. No.	presentation	GCS	precipitating factor	RBS (mg/dl)	pH	HCO3	dka severity	sodium	corrected sodium	pottasium	chloride
1	n, v , stupor	9	inadequate	550	6.9	5	severe	138	147	4.2	94
2	vomiting	13	infection	502	7.1	2.5	moderate	150	159	2.9	80
3	loose stools	15	infection	287	7.2	17	mild	130	133.7	4.7	94
4	n,v	15	not known	572	6.9	8	severe	146/143	155	6	82
5	abdominal pain	13	pancreatitis	520	7	1.6	severe	146	154	6.1	84
6	breathlessnesss	13	infection	580	6.9	7	severe	138	147.6	5.7	114
7	seizures	13	necrotizing pneuonia	484	7.2	11	mild	148/140	155.7	3	77/80
8	leg swelling	15	not known	375	7.2	12	mild	152	157.5	4.5	85
9	v, loose stools	12	infection	480	6.9	5.4	severe	146	153.6	2.9	86
10	fever, wight loss	11	new	586	6.9	1.9	severe	137	146.7	4.7	94
11	vomiting	15	noncompliant	520	7.2	7	mild	137	145.4	4.2	109
12	loose stools	13	noncompliant	302	7.3	7.7	mild	132	136	4.4	103
13	vomiting	15	noncompliant	284	7.2	9	moderate	143	146.7	5	86
14	abdominal pain	15	noncompliant	437	7.157	4.7	moderate	126	132.7	3.7	112
15	breathlessnes	15	noncompliant	351	7.1	6	moderate	135	140	4.2	67
16	breathlessness	15	new	358	7.1	8.9	moderate	134	139.2	4.5	98
17	vomiting , abdominl pain	9	new	394	6.9	6	severe	131	136.9	4.5	111
18	brethlessness	15	noncompliance	485	7.1	9	moderate	133	140.7	4.2	97

sl. No.	presentation	GCS	precipitating factor	RBS (mg/dl)	pH	HCO3	dka severity	sodium	corrected sodium	pottasium	chloride
19	seizures	13	infection/noncompliance	582	7.1	12	moderate	134	143.6	4.4	95
20	breathlessness	13	new	402	7.1	7	moderate	136	142	4.2	102
21	altered sensorium	9	inadequate dose	578	6.9	6	severe	134	143.6	4.1	101
22	vomiting	15	noncompliant	348	7.1	11	moderate	132	137	5	74
23	altered sensorium	3	new	441	7	5	severe	137	143.8	6.6	102
24	altered sensorium	6	noncompliant	484	7	5.2	severe	144	151.7	5	88
25	altered sensorium	6	orbital mucrmycosis	614	7.3	9	severe	146	156.3	4.6	82
26	vomiting	13	sepsis	516	7	9	moderate	121	129.3	4.9	90
27	vomiting	3	noncompliant	543	7.3	7.4	severe	136	144.9	2.9	89
28	abdominal pain	15	noncompliance	600	7	7	severe/mod	138	148	5.4	79
29	abdominal pain	6	new	510	7.3	8	severe/moderate	151	159.2	3.9	92
30	giddiness	6	new	387	7.3	8	severe/moderate	150	155.7	2.9	94

sl. No.	magnesium	phosphorous	calcium	corrected calcium	serum osmolality	urea	BUN	creatinine	HDL	LDL	VLDL	TC	TGL	Hemoglobin	TC	SGOT	SGPT
1	2.1	1	7.7	8.5	313	37	17.27	0.7	20	22	21	63	106	11.9	6800	20	16
2	3	2.3	7.4	8.8	335	40	18.7	1	16	65	19	100	94	10.2	6000	30	27
3	1	3.3	7.9	9.1	279	20	9.3	0.4	32	79	17	119	85	10.3	5700	41	15
4	4 then 2	3.8	6.2/7.3	7.7	336	64	33/29.87	1.5	40	78	71/15	189	355/76	13.8	29300	34	31
5	4	4.9	?4.9	4.8	328	43	20.07	1.4	28	49	137	216	693	10.4	5200	36	21
6	4	2.5	7.1	8.8	317	54	25.2	1.5	54	101	33	188	164	8.2	7800	15	9
7	4 then 5	2.6	7.3/8.4	8.7	334	66	30.8	1.3	56	94	20/15	171	101/76	8	7000	45	21
8	3	2.6	7.4	8.8	328	20	9.33	0.7	21	59	19	99	93	9.8	7000	40	26
9	1	2	?4.5	5.9	322	22	10.27	0.5	18	62	17	94	83	12.2	15500	20	18
10	1.8	2.6	8.2	9.3	310	18	8.4	0.5	27	72	24	123	121	9.5	7800	19	32
11	2.4	2.1	6.6	8.2	308	28	13.07	0.8	29	125	42	196	212	12.4	6300	30	24
12	2	3.8	?3.3	5.1	291	62	28.93	1	23	104	45	155	403	9.5	5600	19	20
13	3	2.4	?5.7	8	314	72	33.6	1.8	10	67	12	90	61	9	4000	31	36
14	6	3.3	6.1	8.3	282	36	16.8	0.8	32	50	20	102	101	10.8	11000	14	14
15	3	2.2	9.2	10.3	300	60	28	1.1	29	102	38	169	190	12	6500	49	50
16	2.2	2.4	8.4	9.2	293	28	13.07	0.6	40	98	30	168	112	13	9600	20	24
17	2.1	2.3	7.2	8.8	290	38	17.73	0.8	18	78	20	116	120	12.9	8400	24	20
18	2	2.5	8.8	9.8	297	28	11.07	0.7	45	102	20	167	98	12.1	7800	19	34

sl. No.	magnesium	phosphorous	calcium	corrected calcium	serum osmolality	urea	BUN	creatinine	HDL	LDL	VLDL	TC	TGL	Hemoglobin	TC	SGOT	SGPT
19	2.3	4.3	9	9.8	311	66	30.8	1.2	38	83.2	25.8	147	129	9	5800	22	24
20	3.1	5	8.1	9.1	300	34	15.87	0.8	23	34	45	102	225	12	6400	19	20
21	2.4	3.8	8.4	9.2	308	46	21.47	1	38	131	90	260	451	11.8	7000	24	28
22	2	2.4	9.2	9.8	289	37	17.27	0.6	41	143	18	202	88	11.4	5400	41	13
23	1.6	0.8	6.6	7.4	306/310	67	20.53/31.27	2.8	34	136	56	226	280	10.2	7000	94	39
24	3.6	1.8	4.4	5.2	333	112	52.27	2	29	47	32	110	112	9.8	10100	32	34
25	3	8.6	3.3	4.4	336	60	28	1.6	28	135	26	189	129	9.2	17000	27	14
26	6	4.5	6.5	7.9	286	91	42.47	2.4	10	47	74	131	371	7.2	19000	18	10
27	1.9	4.4	6.6	7.9	319	100	46.67	1	29	74	38	141	194	10.9	9300	19	12
28	2	6.1	8.1	7.6	321	72	33.6	1.3	51	53	9	113	44	10.8	10200	39	21
29	3.2	1.4	4.2	5.2	357	161	75.14	3.9	24	64	45	129	241	9.8	21000	25	22
30	3	6	5.4	6.8	342	123	57.4	1.9	22	56	56	134	264	10.9	6200	24	30

sl. No.	TB	DB	IDB	TP	ALBUMIN	ALP	HBA1c	complications	hospital stay	outcome	acetone negative
1	0.9	0.4	0.5	5	3	44	14.1	nil	4	discharged	3rd day
2	1	0.6	0.4	5	2.2	81	8	nil	3	discharged	
3	0.8	0.5	0.3	5.2	2.5	52	13.6	nil	3	discharged	
4	0.6	0.3	0.5	6.3	2.1	93	14.3			discharged	2nd day
5	0.9	0.4	0.5	6	4.1	106	13		4	discharged	
6	0.8	0.3	0.5	5.8	1.9	116	12.8			discharged	2nd day
7	1	0.6	0.4	5.3	2.2	102/74	11.7			discharged	2nd day
8	0.8	0.5	0.3	5.4	2.2	153	11.8	nll		discharged	2nd day
9	0.9	0.6	0.3	6.2	2.2	43	12.8		6	discharged	3rd day
10	0.8	0.3	0.5	6.6	2.6	42	13.8		6	discharged	3
11	1	0.6	0.4	5.1	2	33	11.3	nil		discharged	
12	0.9	0.5	0.4	4	1.8	97	12.7	nil	5	discharged	3r day
13	0.9	0.5	0.4	4.9	1.1	42	11.6		3	discharged	2nd day
14	0.9	0.4	0.5	4.5	1.3	111	12.2	nil	5	discharged	3rd day
15	1	0.6	0.4	5.2	2.6	92	12			discharged	2nd day
16	0.9	0.4	0.5	6	3	76	12.2	nil		discharged	2nd day
17	0.9	0.4	0.5	5.1	2	98	12.4			discharged	4thday
18	0.9	0.4	0.5	5.4	2.4	67	13.7	nil		discharged	2nd day

sl. No.	TB	DB	IDB	TP	ALBUMIN	ALP	HBA1c	complications	hospital stay	outcome	acetone negative
19	0.9	0.3	0.6	6.2	3	84	17.1		4	discharged	2nd day
20	0.8	0.3	0.5	5.3	2.8	87	12.3			discharged	2nd day
21	1	0.4	0.6	5.4	3	104	18.4			discharged	3rd day
22	1	0.4	0.6	5.6	3.3	53	10	nil		discharged	2ndday
23	1	0.6	0.4	5.8	3	77	13.7		mechanical	death	3rd day
24	0.9	0.4	0.5	5.9	3	67	12.3	aspiration	mechanical	death	12 hrs
25	1	0.4	0.6	7.2	2.9	185	13.7			death	12hrs
26	1	0.4	0.6	5.5	2.3	70	13.8			death	12hrs
27	0.9	0.5	0.4	5.2	2.4	27	12.5			death	4th day
28	1	0.4	0.6	6.2	4.6	67	14.4	pulmonary		death	12hrs
29	1	0.4	0.5	6	2.8	46	14.2			death	4th day
30	0.9	0.4	0.5	5.4	2.2	54	14.1			death	12hrs

S.no	Name	Op no	Age	Sex	Address	Occupation	Education	Type of dm	Duration of dm	Treatment	Alcohol	Smoking	CO morbid	BMI	RBS	Sodium	Pottasium	Chloride	Magnesium	Phosphorus
1	Noorjahan	32240	50	F	Thanjavur	Housewifesslc	Sslc	Type 2	7 years	OHA	No	No		23	93	146	3.8	81	1.49	3.4
2	Sekar	3228	53	M	Thanjavur	Driver	Sslc	Type 2	1 year	OHA	no	No		32	168	150	3.2	84	1.65	3.8
3	K.rajavel	142581	50	F	Thanjavur	Carpenter	Sslc	Type 1		Insulin	No	No		24	329	136	4.5	78	1.5	4.8
4	Ganesan	54957	50	M	Papanasamcooli	farmer	Illiterate	Type 2		OHA	Yes	Yes		22	175	139	4.8	68	1.87	5.8
5	Suseela	55076	70	F	Thanjavur	Housewifesslc		Type 2	7years	Insulin	No	No		29.4	317	136	4.9	73	1.36	4.5
6	Selvarani	55065	30	F	Elanthakudamcooli		Illiterate	Type 2	2years	Insulin	Yes	Yes		16.5	218	140	4.8	77	4.4	1.48
7	Saraswathi	55078	67	F	Pattukottai	Cooli	Illiterate	Type 2	3months	OHA	No	No		16.6	78	138	4.9	89	5.03	2.03
8	Lakshmanan	55088	60	M	Nagapattinam cooli		Illiterate	Type 2		OHA	No	No		21.4	211	138	4.8	74	1.45	3.7
9	Selvaraj	55060	65	M	Thanjavur	Cooli	Illiterate	Type 2	10 years	Insulin	No	No	Sht	25	156	140	4.6	85	1.69	4.4
10	Govindasamy	55160	76	M	Papanasamcooli	farmer	Illiterate	Type 2	5 years	OHA	No	No		19.9	127	138	4.6	81	1.28	3.9
11	Naffisha	80678	40	F	Thanjavur	Housewifesslc		Type 2	10 years	OHA	No	No		32	132	140	4.8	84	1.72	3.5
12	Arivazhan	217529	59	M	Orathanaducooli		7th	Type 2	5 years	OHA	No	No	Sht	25	98	138	4.8	76	1.42	4.1
13	Jothi	329565	60	M	Orathanaducooli		Sslc	Type 2	1 year	OHA	No	No	Sht	25	108	136	4.6	80	1.7	4.1
14	Thiruneelakandan	27485	72	M	Thanjavur	Cooli	Sslc	Type 2		OHA	Yes	Yes		21	366	138	4.2	17	1.36	4
15	Samikannu	41423	53	M	Thanjavur	farmer	5std	Type 2	1 year	OHA	Yes	Yes		19	165	150	4.8	82	1.5	4.5
16	Balasubramanian	542314	60	M	Thanjavur	Cooli	Sslc	Type 2	15 years	OHA	Yes	Yes		28	312	136	4.8	82	1.6	1.1
17	Chinnaponnu	279563	50	F	Thanjavur	Cooli	Sslc	Type 2		OHA	No	No		21	177	140	4.2	87	1.4	4.1
18	Abima	70735	55	F	Thanjavur	Housewifesslc		Type 2	10years	OHA	No	No		32	186	148	3.8	78	1.5	3.8
19	Murugesan	34838	53	M	Thanjavur	OA	Sslc	Type 2	8years	OHA	Yes	Yes		23	174	150	3.4	86	1.4	3.7
20	Kanaga	563484	60	F	Thanjavur	Coolie	8th	Type 2	1year	OHA	No	No		23	214	148	3.9	102	2.4	3.4
21	Saroja	43709	55	F	Thanjavur	Coolie	illiterate	Type 2	1year	OHA	No	No	SHT	26	70	153	3.2	85	1.53	4.2
22	Kulanthaiammal	522301	70	F	Thanjavur	Coolie	5th	Type 2	3years	OHA	NO	NO	SHT	23	74	148	3.8	108	3.04	5.5
23	Rani	41323	45	F	Ariyalur	Housewifesslc	8th	Type 2	6years	OHA	No	No		20	230	149	3.4	102	2.37	4.6
24	Kumaraguru	32156	43	M	Thanjavur	Welding	10th	Type 2	1week	OHA	No	No	SHT	26	62	152	3.8	107	3.22	4.1
25	Bhuwanweswari	523441	48	F	Thanjavur	Housewifesslc	12th	Type 2	3years	OHA	No	No	SHT	41	44	142	3.6	105	3.2	4.7
26	Sakilabegum	35678	50	F	Seppanavany	Coolie	10th	Type 2	3years	OHA	No	No	SHT	24	342	148	3.6	105	2.71	4.1
27	Amir john	490234	63	F	Seppanavany	Coolie	10th	Type 2	3years	OHA	No	No	SHT	19	345	152	3.4	104	3.01	3.5
28	Rasathi	56785	51	F	Kothily	Housewifesslc	5th	Type 2	3weeks	OHA	No	No		23	70	148	3.3	103	2.88	4.1
29	Abdul muthalif	55031	68	M	shivaji nagar	cooli	12th	type 2	2 years	OHA	NO	NO	SHt	19	141	149	3.4	82	2.99	2.9
30	Akilambal	55043	65	F	Thiruvayar	Housewife 5th		Type 2	2 years	Insulin	No	NO		18	65	150	3.5	105	2.5	4.5
31	Banumathi	55032	56	F	Thanjavur	Housewife	8th	Type2	2years	OHA	No	No		19	107	138	4	105	2.9	4.2
32	Thamaraivalli	55038	61	F	Thanjavur	Housewife	Illiterate	Type 2	3years	OHA	No	No	SHT	20	177	146	3.2	103	2.8	4.6
33	Chinnaponnu	55064	50	F	Thanjavur	Housewife	Illiterate	Type 2	1week	OHA	No	No		21	185	145	3.9	100	3	3.8
34	Natarajan	55084	56	M	Thanjavur	cooli	Illiterate	Type2	1year	OHA	NO	NO	SHT	27	98	145	3.8	105	2.85	3.4
35	Kaliyaperumal	89670	67	M	Vallam	Cooli	7th	Type2	2years	OHA	NO	NO		25	117	152	3.1	106	2.76	3.9

S.no	Calcium	Corrected calcium	Urea	Creatinine	HDL	LDL	VLDL	TC	TGL	Hemoglobin	Tc	SGOT	SGPT	TB	TP	Albumin	ALP	HBA1c
1	8.6	8.3	35	0.6	35	130	38	203	191	14.9	4000	13	13	1	7.1	4.4	33	6.3
2	8.6	8.5	31	0.6	35	54	37	126	187	11.6	4300	13	7	1.1	8.2	4.1	57	9.1
3	8.5	8.3	34	0.9	35	131	52	84	187	12.8	6000	13	13	0.9	8.3	4.2	50	11
4	8.3	8.7	54	1.3	16	130	83	229	416	13.1	4300	13	18	0.9	7.1	3.5	158	7.5
5	8.3	8.8	67	0.8	32	90	60	187	302	13.1	6800	13	13	0.8	7.1	3.4	81	10
6	8.5	9.1	27	0.3	46	141	24	211	122	15.3	9400	13	7	0.9	7.5	3.2	63	10
7	10.2	10.4	34	1	40	54	71	165	356	11	6200	13	15	1	6.9	3.7	37	5.1
8	8	8.6	30	0.4	28	122	51	201	253	11.5	5200	13	5	0.8	7.2	3.2	83	11
9	8.8	8.6	34	0.7	30	87	67	184	330	12.6	3400	13	13	0.7	8	4.3	56	8.3
10	8.6	9.1	75	1.4	34	93	21	148	105	15.3	5800	13	10	1	6.8	3.4	44	5.1
11	8.2	8.8	34	1.3	37	108	65	148	275	14.3	6300	13	9	1	6.5	3.3	51	6.4
12	8.3	8.1	59	1.4	48	110	21	214	152	10.6	5700	13	3	0.8	8	4.2	52	6.6
13	8.6	8.4	32	0.6	31	84	56	171	278	11.8	5000	13	13	0.9	7.7	4.2	41	6.6
14	8.8	8.9	35	0.8	45	110	21	176	105	10.9	7300	13	5	0.9	7.8	3.9	52	11
15	9.2	8.9	31	0.6	58	195	29	176	144	9.5	9000	13	6	1	8.3	4.4	64	6.8
16	8.7	8.4	29	0.6	53	80	24	157	121	10.7	6700	13	14	0.8	8.2	4.5	68	12
17	9.1	8.7	29	0.7	36	94	15	145	73	13.3	10000	13	9	0.9	8.1	4.5	51	6.2
18	8.7	8.3	35	0.9	39	135	53	225	265	10.9	7700	13	13	0.9	8.1	4.5	52	11
19	8.7	8.4	33	0.8	35	72	22	129	108	12.1	8200	13	6	0.9	7.6	4.4	26	10
20	8.7	9.3	28	0.6	61	137	16	214	81	12	5600	13	10	1	6.5	3.3	44	7.4
21	7.5	7.7	27	0.7	51	57	20	128	102	10.7	5100	13	11	1	6.5	3.8	33	6.5
22	7.7	8.2	83	2	41	77	33	151	164	10.4	6200	13	6	1.1	6.8	3.4	33	5.2
23	7.6	8.1	21	0.5	45	88	20	153	99	11.7	8000	13	7	0.8	7	3.4	75	5.6
24	8.3	8.5	46	0.9	41	178	66	285	330	12.8	11900	13	10	0.8	7.1	3.7	54	5.9
25	8.9	9.4	31	0.6	27	112	30	169	150	11.2	8900	13	5	0.9	7.2	3.4	36	7.8
26	7.6	8.2	61	1.7	50	130	26	204	130	9.1	11000	13	5	0.8	6.4	3.2	71	10
27	8.7	9.1	38	1.1	41	77	42	160	212	12.4	7600	13	7	0.8	6.9	3.5	55	10
28	8.6	8.9	28	0.6	47	117	26	190	132	8	6900	13	8	0.9	7.4	3.6	56	7.2
29	8.2	8.3	29	0.8	44	103	18	165	90	13.6	8700	13	8	1	7.7	3.9	77	7.8
30	8.2	9.1	32	0.4	14	93	23	130	113	11	10600	13	7	0.9	6.6	2.9	77	7.8
31	7.9	8.1	32	0.8	42	108	37	187	187	13.2	8500	13	7	0.9	7.7	3.7	44	12
32	7.9	8.4	30	0.7	36	104	17	157	84	12.5	6000	13	4	1	6.8	3.4	34	10
33	8.4	9	31	0.6	53	139	39	231	195	9.1	5900	13	5	0.9	6.3	3.2	53	12
34	7.6	8.3	44	2	35	120	56	211	281	11.1	4300	13	7	0.9	6.5	3.1	65	5.6
35	7.6	8.2	49	1.4	31	168	22	221	111	9.4	7100	13	6	1	7.6	3.3	59	6.1